COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council

December 21, 2001

Via US Mail and E-mail

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency (EPA)
P.O. Box 1473
Merrifield, VA 22116

Re: Formic Acid and Formates Panel, Consortium No. [redacted]
HPV Chemical Challenge Program Submission
Formates Category Justification and Testing Rationale

Dear Administrator Whitman:

The Formic Acid and Formates Panel of the American Chemistry Council is pleased to submit the subject documents to EPA's HPV Chemical Challenge Program (Program) as our initial test plan for a category covering three chemicals (methyl formate, sodium formate and calcium formate). The Formic Acid and Formates Panel includes the following member companies that are sponsoring these chemicals under the Voluntary HPV Chemical Challenge Program: BASF Corportion, Bayer Corporation, Celanese, GEO Specialty Chemicals and Hercules Inc.

This submission includes the following documents:

- Formic acid robust data summaries in IUCLID format;
- Methyl formate robust data summaries in IUCLID format;
- Sodium formate robust data summaries in IUCLID format;
- Calcium formate robust data summaries in IUCLID format; and
- Test Plan for Formates.

Data on formic acid are used to support the conclusions reached for the formates category. Although the ACC Formates Panel is not sponsoring formic acid under the HPV Chemical Challenge Program, an European consortium is sponsoring the chemical under the ICCA Initiative.

This submission is also being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov
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If you require additional information, please contact Has Shah, Formic Acid and Formates Panel Manager at (703) 741-5637 or has_shah@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Attachments

cc: C. Auer, EPA/OPPT
B. Leczynski, EPA/OPPT
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U.S.EPA HPV Chemical Challenge Program

Test Plan for the

Formates Category

Formic Acid* CAS#:64-18-6
Sodium Formate CAS#:141-53-7
Calcium Formate CAS#:544-17-2
Methyl Formate CAS#:107-31-3

Submitted by:
American Chemistry Council
Formic Acid and Formates Panel

Submitted to:
U.S. Environmental Protection Agency

Prepared by:
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December 20, 2001

* Formic Acid is being reviewed as an ICCA chemical and is not formally a HPV chemical.

Table of Contents

Executive Summary

The HPV category "Formates" is proposed and justified to comprise the four HPV chemicals:

- Formic acid
- Sodium formate
- Calcium formate
- Methyl formate

These chemicals are used in many diverse applications including agriculture, leather production, grout and concrete mixes, steel making, as solvents and as chemical intermediates.

Experimental evidence is presented to demonstrate that the formate ion is the prime determinate of toxicity for all members of this category. Methyl formate, which is a volatile solvent, may at first glance appear to be an outlier; however, it fits nicely into this category since it is rapidly hydrolyzed *in vitro* and *in vivo* to formic acid and to methanol. Methanol systemic toxicity is known to primarily be a result of formate produced by the biological oxidation of methanol. Pharmacokinetic data indicate that methyl formate is transformed very rapidly into formic acid and methanol in the body with a half-life on the order of several seconds. In the environment, this transformation is facile at neutral pH and increased at slightly basic pH levels.

Although the physicochemical characteristics of these materials vary from volatile liquid to nonvolatile solids, they share most properties that relate to potential impact on the environment and health. All are readily biodegradable and present little or no bioaccumulation or bioconcentration. Although initial environmental distribution varies among these materials, the ultimate fate as carbon dioxide is shared among all members.

Adverse effects on environmental organisms are minimal for the category. Formic acid has specific potential adverse effects by virtue of its strong acidic properties and methyl formate possesses a solvent-narcosis activity prior to hydrolysis. After hydrolysis or neutralization, all materials converge to the low-hazard formate ion, which itself is

readily converted to carbon dioxide in the environment by biodegradation or photo oxidation.

The acute toxicity of all materials is low with no special hazards. As with the environmental effects, formic acid has additional health hazard due to its strong acid properties and methyl formate can produce solvent-narcosis at high concentrations.

Genotoxicity testing results are largely negative but additional information is desired to fulfill the HPV chromosome aberration endpoint of methyl formate and *in vitro* testing is proposed. Low-level exposures to formates are not considered a health concern because formate is a normal component of the human body and is contained naturally in many foods.

After repeated dosing by inhalation or by drinking water, few systemic effects have been observed for formates. A 13-week inhalation study of formic acid in rats and mice provides strong evidence of formate's low systemic hazard. Chronic and multigenerational studies of sodium and calcium formate indicate low chronic, reproductive and developmental hazard; however, these studies are not well documented. Although these studies are of value, the confidence in the results is lower than for the acute hazard. A developmental toxicity study using sodium formate as a model formate is recommended.

Testing Plan

Data for most of the HPV endpoints are either available or can be readily estimated with sufficient certainty for most of the HPV endpoints for these chemicals. Formic acid data needs are being addressed by an EU consortium under the ICCA Initiative. In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to fill certain data gaps. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of

animal welfare concerns to minimize the use of animals in the testing of chemicals. The following studies are planned to strengthen the data set for toxicological information of formates:

- *In vitro* chromosome aberration for methyl formate
- Developmental toxicity for sodium formate

Testing Plan in Tabular Format

Formates Category	Formic Acid*	Calcium Formate	Sodium Formate	Methyl Formate		
HPV Endpoint						
					Codes	
Physical Chemical						
Melting Point	D	D	D	D	*D*	Data Available
Boiling Point	D	D	NA	D	*E*	Estimate
Vapor Pressure	D	NA	NA	D	*S*	Surrogate
Water Solubility	D	D	D	D	*T*	Testing
Partition Coefficient	D	NA	NA	D	*NA*	Not applicable
Environmental & Fate						
Photo-Degradation	E	NA	NA	E		
Water Stability	NA	NA	NA	E		
Transport	E	E	E	E		
Biodegradation	D	S	D	D		
Ecotoxicity						
96-Hour Fish	D	D	D	D		
48-Hour Invertebrate	D	E	D	D		
72-96-Hour Algae	D	E	D	D		
Toxicity						
Acute Oral	D	D	D	D		
Acute Inhal	D	NA	D	D		
Acute Dermal	NA	NA	NA	D		
Repeated Dose	D	D	D	S		
Reproductive**	T	S	T	S		
Developmental	T	S	T	S		
Genetic Toxicology *in vitro*	D	D	D	D		
Genetic Toxicology *Clast*	D	S	D	T		

* Formic acid is being addressed under ICCA by an EU consortium.

** Specific reproductive tests will not be conducted as this endpoint may be filled by a combination of a repeated-dose/subchronic study and a developmental toxicity study.

Overview and Justification of Category

Chemicals in the Category

This HPV category is composed of formates and consists of four HPV chemicals.

1. Formic Acid
2. Sodium formate
3. Calcium formate
4. Methyl formate

Formic acid is an ICCA chemical and a separate document is being prepared in the EU for assessment under the OECD/SIDS program. Data on formic acid will be reviewed here because it is the base member of the category and has a rich data set. Other chemicals will be discussed in this document as they relate to the four main compounds. For example, ethyl formate is a close relative of methyl formate and methanol is an environmental and physiological hydrolysis product of methyl formate. Information on biological activity of sodium and calcium ions are also relevant to defining hazard from the two salts.

Rationale for Class

Grouping of similar chemicals into classes is encouraged to conserve resources and reduce animal usage in the HPV Challenge Program. The Formates constitute a category where grouping is readily justified and where viewing the group in this way enhances understanding of the potential toxicity of all members.

There are several possible ways of grouping chemicals in the HPV program to form categories. Ultimately, the best grouping is one that will allow prediction and understanding of the toxicity of similar members of the category based on structure and physical or chemical properties. Similar mechanisms of action and metabolic profiles strengthen the coherence of a category. This grouping of formates fulfills the condition of similar mechanisms and metabolism and provides a logical category. Although the

members have varying physical properties, the contribution of these physical properties to the hazard can be readily estimated from chemical principles.

The primary logic of treating these as a group stems from the high probability that the SIDS toxicity endpoints will be primarily mediated by the formate moiety that all members have in common. Certain differences are recognized which are important to the acute health effects, these include pH, physical state, and likely routes of exposure. On the other hand, the more important long-term toxic effects from low-level exposure are likely related primarily to blood and tissue levels of formate. All four are clearly sources of systemic formate.

Oral exposure to low levels of formic acid, sodium formate or calcium formate are expected to result in essentially identical formate uptakes. The ionization state (neutral or anionic) in the gastro intestinal tract will determine the absorption. The form is determined almost solely by the pKa (3.74) of the formate anion and the pH of the GI tract. Provided excessive amounts of any of these three are not ingested such that the pH is altered (or solubility is delayed), the normal GI pH will result in essentially identical ratios of formic acid:formate. Thus, the absorption, distribution, metabolism, and toxicity of these three formates are anticipated to be identical at low oral exposure levels. Since neither the hydrogen ion, nor the sodium ion, nor the calcium ion is considered highly toxic, differences in toxicity from low-level oral exposure are not anticipated if converted to a mole of formate basis.

Methyl formate is known to be rapidly hydrolyzed by serum and liver esterases (1) and in body fluids (2) to methanol and formate (formic acid). Methanol is rapidly metabolized in the body to formate. Thus, after absorption, hydrolysis and oxidative metabolism of the methanol moiety of methyl formate, all that remains is formate. In practice, the route of exposure for methyl formate is likely to vary from the other materials. For example, since methyl formate is not a strong irritant, is low molecular weight, uncharged and volatile; dermal absorption and inhalation are more likely to be significant routes of exposure.

A PBPK-like toxicokinetic model was recently developed for methyl formate in humans and has been validated using data from volunteers exposed to methyl formate (1). The salient features of this model that validate the inclusion of methyl formate in the formates class are the estimation of the rate constant (K_{MF}) for methyl formate hydrolysis *in vivo* and the demonstration that the methanol formed is metabolized to formate. The estimated

first order rate constant for hydrolysis of methyl formate derived for the model is 6.7 min^{-1}, which corresponds to an *in vivo* half-life of only 6.1 seconds. This indicates that methyl formate hydrolysis is almost instantaneous in the body and it is unlikely that there is significant distribution of methyl formate except as methanol and formic acid. The formed methanol is subsequently oxidized to formate, which is known to be the causative agent for much of the reported methanol systemic toxicity (3). It is therefore prudent when considering systemic toxicity, to treat methyl formate as formate.

In support of a common mechanism of toxicity, the rat oral LD_{50} when calculated in units of milli-equilivants formate per kilogram bodyweight is very similar across the category. Formic acid shows more toxicity, which is anticipated due to its acidity. Methyl formate shows the lowest toxicity on this basis. The lower acute toxicity of methyl formate is possibly due to either/or the slower conversion of methanol to formate altering the formate toxicokinetics or the excretion of methanol or methyl formate via the lungs. In addition, the higher oral LD_{50} of methanol itself (>5000 mg/kg) is in accord with this proposed mechanism for reduced methyl formate oral acute toxicity. Overall, the correlation of LD_{50} with milli-equilivants formate is very good and supports a common mechanism for acute toxicity.

Material	Mol Wt	# Formates	LD_{50}	LD_{50} in meq/kg
Formic acid (4)	46	1	730-1830	16 - 40
Calcium formate (5)	130	2	2700	38
Sodium formate (6)	68	1	>3000	>44
Methyl formate (7)	60	2	1500	50

Another piece of supporting evidence for inclusion of methyl formate in the category comes from the LD_{50} of ethyl formate, which is reported in IUCLID as 1850 mg/kg (8) and as 4490 mg/kg (9). The expectation, based on the assumption that methyl formate is acutely toxic due to its metabolism to formate, is that ethyl formate would have a higher LD_{50} by about 2-3 fold since it is metabolized to ethanol and formate and the ethanol goes on to

acetate rather than formate. The experimental evidence fits reasonably well in this case. Propyl formate, likewise, is reported to have an LD_{50} of 3980 mg/kg in the rat by oral administration also showing a fit of these simple formate esters in the same category with formate salts regarding acute toxicity (10).

A toxicokinetic model for methyl formate exposure and excretion has been recently developed and validated (11). The model indicates that the initial metabolites of methyl formate are formic acid and methanol. Methanol is both excreted and converted to formic acid. Formic acid excretion kinetics in the urine was reported to be controlled by a saturatable urinary reabsorption of formic acid.

It is known that methanol toxicity is largely determined by its metabolism to formic acid (3). The toxic effects of methanol and metabolic acidosis are mainly or completely a result of the extreme elevation of blood formate resulting from metabolism of methanol to formic acid. Formate mediated methanol toxicity also accounts for the species difference of methanol toxicity wherein primates, which are relatively poor at metabolizing formate, are more sensitive to the toxic effect of methanol than are rodents, which metabolize formate more quickly (12). Investigations of methanol toxicity also led to the finding that folate deficiency exacerbates methanol toxicity. The mechanism was determined to be through tetrahydrofolate-mediated metabolism of formate to carbon dioxide. In this mechanism, formate binds to tetrahydrofolate (THF) and the complex is oxidized to carbon dioxide by the enzyme formyl-THF (13). Therefore, lack of sufficient folate leads to a reduced rate of formate metabolic clearance.

Because of the role of formate in methanol toxicity, much of the information derived from the study of methanol is applicable to understanding the toxicity of formates. In addition, this connection of formate with methanol toxicity strengthens the inclusion of methyl formate as a member of the HPV formates category relative to health effects.

Effects on environmental organisms at low levels are expected to primarily be a result of the formate ion. Methyl formate, being an organic ester, is anticipated to have direct acute solvent-like effects on environmental organisms at high concentrations and these narcotic-like effects are considered separately. Environmental hydrolysis of methyl formate at pH 7 to 9 is known to be a facile process yielding methanol and formic acid (14). At pH 8 and 25˚ C the hydrolytic half-life of methyl formate in aqueous solution is

calculated to be 5.3 hours based on the published K_b. Under typical environmental conditions, formic acid that is formed by hydrolysis will react with water to quantitatively produce formate anion. Methanol that is produced will be biologically oxidized via formaldehyde to formate and finally carbon dioxide. Thus, methyl formate fits in the category relative to environmental effects.

Available data for aquatic toxicity support the proposed categorization and are given in the table below. As discussed above, methyl formate is anticipated to differ from the others due to the ester moiety dominating the acute toxic effects. Formic acid is anticipated to differ by virtue of its acidity. Calcium ion is known to be of low aquatic toxicity (15); therefore, calcium formate should fit into the paradigm adequately.

Material	LC_{50} or EC_{50} (mg/L)		
	Fish	Daphnids	Algae
Formic acid (4)	46-175	120-150	25
Calcium formate (5)	>1000	ND	ND
Sodium formate (6)	>5000	>1000	~1000
Methyl formate (7)	120	>500	190-240

In summary, the category approach is well supported for the proposed "Formates" category comprised of formic acid, sodium formate, calcium formate and methyl formate. The environmental and health effects of the ionic formates are primarily determined by the formate moiety. Methyl formate is rapidly converted to formic acid and methanol, which is subsequently converted to formate. Much of the environmental and health effects data developed for any member of the category will apply across the category. The category approach is justified to save resources including the use of experimental animals.

Production, Uses and Exposures

All of these formates are produced or imported over a million pounds per annum into the United States. The uses and potential exposures vary across the category. It should be

noted that formates are naturally occurring in the body and in many foods. The introduction to the NTP 13-Week study report summarizes the natural occurrence of formic acid as follows: "Formic acid, first described by Fisher in 1670 in the products resulting from the distillation of red ants (16), occurs in both natural and man-made sources in the environment. A constituent of ant, wasp, and bee venom, formic acid also occurs in mammalian muscle tissue, sweat, and urine. It is found in plants, such as in the needles of the Douglas fir, and in unripened grapes, peaches, raspberries, strawberries, petitgrain lemon, and in bitter orange (17). It also is present in many foods (18), e.g., fruits (20 - 40 ppm), fruit juices (30 - 100 ppm), fruit syrups (650 - 1630 ppm), honey (20 - 2000 ppm), wines (1 - 340 ppm), coffee, roasted (1350 - 2200 ppm), coffee, extracts (2000 - 7700 ppm), evaporated milk (30 - 400 ppm), and cheese (20 - 200 ppm) (19)." (20).

Methyl formate has also been detected in foods. Reports describe its occurrence in tomatoes (21), apples (22), and coffee (23). Therefore, oral exposure through ingestion of common foodstuffs will contribute to human exposures.

Formic Acid

In the *Kirk-Othmer Encyclopedia of Chemical Technology* (24) it is stated that there are three main processes used to produce formic acid. The first is by acid-hydrolysis of formate salts that are in turn by-products of other processes. The second is as a co-product with acetic acid in the liquid-phase oxidation of hydrocarbons and the third is by carbonylation of methanol to methyl formate, followed by direct hydrolysis of the ester or through formamide. Worldwide production of formic acid was estimated at 330,000 tones per annum in 1988 with US production estimated at 13,000 tones per annum (25).

Formic acid is used in textile dying and finishing, as a chemical intermediate, in leather processing, in rubber manufacture, as a catalyst in hydrocarbon-formaldehyde resins & phenolic resins and as a plasticizer for vinyl resins. It also is reportedly used in the electroplating industry, as an antiseptic in wine and beer brewing, as a preservative in animal feed additives, as a component of cleaning solutions, as a wire stripping compound, in the preparation of bare wires for soldering, as a laundry sour and as an oil well acidifying agent (26).

The primary use worldwide is as a silage additive. This use is more prevalent in Europe than the US. Formic acid application to fresh-cut grasses prior to ensilation enhances the nutritional value of the produced silage. Lactic acid production is enhanced while the undesirable butyric acid production is avoided. Formic acid can also be used as an additive in animal feeds where it has anti-bacterial activity. Use as a chemical intermediate includes the preparation of formate esters used in flavors and fragrances and in the synthesis of aspartame. U.S. Production in 1975 was reported as 28 million kg (24).

The United States usage pattern of formic acid was described in 1965 by SRI International as 55 percent used in textile dyeing and finishing; 15 percent as an intermediate for formates; 10 percent in leather tanning; and 20 percent in miscellaneous applications (26). A more recent estimate of usage from the Chemical Products Synopsis in 1985 indicates shifting usage with textile dyeing and finishing at 21 percent, 20 percent in pharmaceuticals, 16 percent in rubber intermediate, 15 percent in leather and tanning treatment, 12 percent in catalysts, and 18 percent in miscellaneous uses including oil well acidizing (26). The 2001 Chemical Economics Handbook does not break the usage pattern into percentages but suggests a similar distribution of uses. It also adds the following uses, in the manufacture of epoxidized soybean oil and as an active ingredient in commercial cleaning products (27).

Exposure to formic acid may occur by inhalation, dermal absorption or ingestion. As formic acid is strongly irritating, it is assumed that exposure by the inhalation or the dermal route is self-limiting. Oral ingestion of foodstuffs with naturally occurring formic acid content is not thought to be a health concern and ingestion is an unlikely route relative to industrial exposure where most of the US production is consumed. No information on exposure levels was available for review.

In 1976, under contract to the FDA, the Federation of American Societies for Experimental Biology (FASEB) produced a “GRAS Document” covering formic acid, sodium formate and ethyl formate. The conclusion of this report was that the use of formic acid and sodium formate as an ingredient of paper and paperboard food packaging material does not present a hazard (28).

The FDA allows the use of formic acid as a food additive permitted for direct addition to food for human consumption as a synthetic flavoring substance and adjuvant in accordance with the following conditions: 1) the quantity added to food does not exceed

the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food, and 2) when intended for use in or on food it is of appropriate food grade and is prepared and handled as a food ingredient (29). In addition, the FDA permits the use of formic acid as a preservative in hay crop silage in an amount not to exceed 2.25% of the silage on a dry weight basis or 0.45% when direct-cut. The top foot of silage stored should not contain formic acid and silage should not be fed to livestock within 4 weeks of treatment (30).

Sodium Formate

Sodium formate is produced by the reaction of carbon monoxide with sodium hydroxide and as byproduct in the production of pentaerythritol. U.S. Production in 1975 was reported as 15 million kg. (31).

Sodium formate is used as an intermediate in the production of formic acid, oxalic acid and a few other chemicals. It is used in electroplating and textile production, in the tanning of leather and as a reducing agent (31). Other uses are for gas scrubbing, as an oil-well drilling fluid additive and a small quantity is used as an ingredient in liquid detergents. The major current uses are in leather tanning, gas scrubbing and as an oil-well drilling fluid additive (32).

Sodium formate is affirmed as GRAS by the FDA as a constituent of paper and paperboard used for food packaging (33).

Exposure to sodium formate is restricted to workers in chemical plants producing the material, chemical workers using it as an intermediate, textile workers, electroplaters, leather tanners, workers using it for gas scrubbing and as an oil-well drilling fluid additive, and minor consumer dermal exposure from its use in liquid detergents. Since it is not volatile, inhalation exposure is restricted to conditions where particulate material may be suspended in air and inhaled. As an ionic solid, dermal exposure will not result in significant systemic exposure.

Calcium Formate

Calcium formate is prepared from the high-temperature and high-pressure reaction of calcium hydroxide and carbon monoxide (34). It is also available industrially as a by-product from the preparation of pentaerythritol and other polyhedric alcohols and of disodium dithionite (24).

Calcium formate is used as a preservative for silage and as a food preservative. It also finds use as a component of drilling fluids and lubricants, as a binder for fine-ore briquets, in the tanning of leather and in flue gas scrubbing (34). Calcium formate is added to feed and premixes for piglets and calves as an organic acid to stabilize the digestive process (35). It also finds use as a nonchloride accelerator used to reduce the setting time of concrete and similar materials (36). Use in grouts and concrete products are major current uses in the U.S. for calcium formate.

Exposure to calcium formate appears to be restricted to workers in chemical plants using it as an intermediate, or as a component of grout and concrete mixes, farm workers using it to treat silage and potentially workers preparing and dispensing feed where it may be used as an additive. Since it is not volatile, inhalation exposure is restricted to conditions where particulate material may be suspended in air and inhaled. As an ionic solid, dermal exposure will not result in significant systemic exposure.

Methyl Formate

Reported methods for the preparation of methyl formate are the reaction of methanol, carbon monoxide and steam, over a charcoal or sodium methoxide catalyst at 200 degrees C and 200 atmospheres of pressure; by esterification of formic acid and methanol and by heating methyl alcohol with sodium formate and hydrochloric acid (37).

Methyl formate is used as a solvent and a chemical intermediate, a fumigant and larvicide for tobacco, dried fruits, cereals and other foods, and as a high-boiling refrigerant (37). Other reported uses are as a solvent for cellulose acetate (38) and as a catalyst and binding agent for core sand in the production of mold cores in iron foundries where it has replaced dimethylethylamine (39).

Human Experience and Considerations

General

Humans are known to accumulate toxic formate more easily than non-primate experimental animals due to their reduced capacity to metabolize formate to carbon dioxide. Much of this information comes from the study of methanol toxicity where humans have greater sensitivity than most animals and show ocular toxicity while rodents do not. The enhanced methanol sensitivity in large part is a result of the biological oxidative conversion of methanol to formic acid resulting in a metabolic acidosis (and ocular effects) not seen in most lower-animals. The accumulation of formate in humans is due to a relative deficiency in formate metabolism as compared to most experimental animals, related partly to a low hepatic tetrahydrofolate (H4 folate) levels in humans. There is an excellent correlation between hepatic H4 folate and formate oxidation rates within and across species. Humans possess low hepatic H4 folate levels and demonstrate low rates of formate oxidation and the accumulation of formate after methanol exposure (40).

Formic Acid

In the industrial setting formic acid is know to be a severe skin, mucus membrane, eye and respiratory tract irritant; however, few other adverse effects have been definitively associated with industrial exposures (26). Since formic acid is naturally occurring in many foods and as formate is a normal constituent of intermediary metabolism (41), low level systemic exposure is not likely to result in adverse effects.

Intentional ingestion (overdoses) are reported to produce salivation, vomiting (which may be bloody), a burning sensation in the mouth and pharynx, diarrhea, and severe pain. Circulatory collapse may follow, causing death (42). Ellerhorn's Medical Toxicology notes that formic acid ingestions are unique in their ability to cause death after a prolonged course of classical acid-induced gastrointestinal damage. Ingestions of less than 10 grams by children have led to superficial oropharyngeal burns with the children recovering. In adults, ingestions exceeding about 50 grams were generally fatal with lesser doses resulting in superficial oropharyngeal burns, hematemesis, hepatotoxicity, ulcerations and perforation of the gastrointestinal tract (43).

Twelve farmers exposed to formic acid for eight hours in silage making were examined for effects on calcium excretion and renal ammoniagenesis. Eight of the subjects were exposed below 9 mg/m^3 (MAK value) and four were exposed at or above this level. Exposure was associated with increased renal ammoniagenesis and urinary calcium excretion at 30 hours post exposure. It was speculated that these biochemical effects could be explained by the interaction of formic acid with the oxidative metabolism of renal tubular cells. The authors concluded that current hygienic exposure limits might not entirely protect formic acid exposed individuals from renal effects (44).

Exposure limits for formic acid are (45):

- ACGIH TLV: 5 ppm; 9.4 mg/m3 (as TWA); 10 ppm; 19 mg/m3 (as STEL) (ACGIH 1996)
- MAK: 5 ppm; 9 mg/m3; (1995).
- OSHA PEL: TWA 5 ppm (9 mg/m3)
- NIOSH REL: TWA 5 ppm (9 mg/m3)
- NIOSH IDLH: 30 ppm

Sodium Formate

Reports of human experience to exposures of sodium formate are very limited. In Gosselin et al. (46) the entry for formic acid and salts, lists for sodium formate: "sodium formate appears to have a low toxicity (10 g by mouth without ill effects in man)". This report is consistent with the relatively low toxicity of formic acid especially considering sodium formate is not acidic. As noted under formic acid human experience, formate is a normal constituent of intermediary metabolism and low-level systemic sodium formate exposure is probably inconsequential.

No occupation exposure standards were located for sodium formate.

Calcium Formate

No human experience information was available for inclusion and no occupation exposure standards were located. As noted in other sections, formate is a normal

constituent of intermediary metabolism and low-level systemic calcium formate exposure is probably inconsequential.

Methyl Formate

Exposure to methyl formate is believed to occur primarily by inhalation due to its volatility. Dermal exposure is also expected to result in systemic uptake; however, dermal exposure is thought to be very limited as methyl formate, to the best of our knowledge, is only used in industrial settings.

Methyl formate vapor exposure has been reported to produce nasal and conjunctival irritation, retching and CNS depression (37). Recently exposure of human volunteers at 100 ppm was shown to be associated with an increase in the subjective feeling of fatigue without impairment of neurobehavioral performance (47). A study of exposure and neurobehavioral endpoints was recently reported in a foundry. Although the measured exposure exceeded the MAC value of 400 ppm on some occasions, there were no measurable neurobehavioral changes in this group of 10 workers (48).

Exposure limits for methyl formate are (49):

- ACGIH TLV: 100 ppm; 246 mg/m^3 STEL 150 ppm (ACGIH 1996).
- OSHA PEL: TWA 100 ppm (250 mg/m^3)
- NIOSH REL: TWA 100 ppm (250 mg/m^3) ST 150 ppm (375 mg/m^3)
- NIOSH IDLH: 4500 ppm

Physicochemical Information

The physicochemical properties of this class are dependent on the physical form and ionization status. Properties required under HPV are either known or can be easily extrapolated for all class members.

Methyl formate is the only true neutral organic molecule in this class, it is a low-boiling volatile liquid, and its physicochemical properties relevant to HPV are known.

Formic acid is also a liquid but much less volatile. On dissolution in water it partially ionizes according to its pKa and the resulting pH of the solution to formate ion. The IUCLID summary notes that there is a discrepancy in the octanol-water partition coefficient values in the literature. This is not surprising as the partitioning is pH and hence concentration dependent. The conclusion, however, is that the equilibrium favors water for both the ionized and non-ionized forms; thus, the Po/w is not definitively known (and may not be directly measurable) but the available information is considered adequate for the HPV Program endpoint.

Both calcium and sodium formate are water-soluble salts of formic acid. As salts, they are solids and essentially non-volatile. Because they are salts of formic acid, the octanol-water partition coefficients are pH dependent and not definitive without specification of concentration or pH. They both favor water and are sufficiently well established for the needs of HPV.

	Physical State	Boiling/Melting Point	Vapor Pressure (20˚)	Water Solubility	Log Ko/w
Formic acid (4)	Liquid	100.6˚ C	42 hPa	Miscible	-0.54
Methyl formate (7)	Liquid	32.3 ˚ C	644 hPa	300 g/L	-0.21
Sodium formate (6)	Solid	253 ˚ C	Nil	550 g/L	ND
Calcium formate (5)	Solid	>300 ˚ C	Nil	160 g/L	-2.47

Summary and Recommendations for Physicochemical Information. All parameters have adequate data for the purposes of HPV. No additional testing is recommended.

Fate Information

Distribution in the environment is anticipated to be the same for formic acid and its sodium and calcium salts provided the pH is equivalent in the environment. The proper calculation of distribution at neutral pH values is to use the properties of the ionized form. The Mackay level III model contained in EPIWIN suggests that the majority of

any of the formates entering a waste water plant will be contained in the effluent. In the case of methyl formate, about 10 percent of the material will likely be lost to air. As all of these formates are readily biodegradable, the actual effluent output will be dependent upon several factors with residence time, temperature and acclimation predominating. Relative to the HPV program, it can be concluded that formic acid, sodium formate and calcium formate will distribute almost exclusively to water where biodegradation will occur with no bioaccumulation. Methyl formate will distribute to water and air where it will photodegrade (air) or biodegrade (water) with little or no bioaccumulation.

As a category, the fate of all of these materials in the environment is dependent primarily upon the fate of the formate ion. Methyl formate is known to break down rapidly to formic acid and methanol. Under aerobic conditions, methanol will oxidize through formate to carbon dioxide. Sodium and calcium cations are stable in the environment but are considered innocuous after dilution. Formate anion is known to be readily biodegradable (50).

All four materials have been tested for aerobic biodegradation and found to be "readily biodegradable" by the OECD criteria (see robust summaries). Although the quality of the tests varies, the consistency and structural similarity indicate that the formate moiety and the methyl moiety are readily biodegraded.

Photodegradation in the atmosphere is reduced by the category approach to a consideration of the photodegradation of formic acid and methyl formate. Sodium formate and calcium formate are not volatile; however, under acidic conditions they will be converted to volatile formic acid that will undergo atmospheric photodegradation.

The rate of reaction of atmospheric hydroxyl radical with formic acid is known and at the default (5.0×10^5 molecule per cubic centimeter) concentration of atmospheric hydroxyl radicals, a $t_{1/2}$ of 35 days is predicted (based on a 24-hour day, see robust summaries for formic acid).

Methyl formate has an experimentally measured reaction rate constant with hydroxyl radicals (given in the APOWIN 1.90 tables comparing estimated to actual values) and

using the current EPA default of 1.5 E^6 hydroxyl radicals per cubic centimeter a $t_{1/2}$ of 47 days (based on a 12-hour day)(7).

Summary and Recommendations for Fate

All fate parameters for all members of the category have adequate information to fulfill the HPV Program requirements. No testing is recommended.

Effects on the Environment

Fish, Invertebrates and Aquatic Plants

The effects of formates on fish, invertebrates and aquatic plants either are known or can be predicted by the category approach and the structures of the materials. In addition a major environmental impact study of sodium formate was conduced by Transport Canada at the Halifax airport in support of the use of sodium formate as a deicing compound on runways (51). The results of this study indicated that the use of sodium formate over the winter of 1991-2 at Halifax International airport had minimal effects on the adjacent vegetated soils or on monitored test streams. In this study, multiple tons of materials were used on a taxiway and extensive environmental quality monitoring was conducted on surface (including aquatic organisms) and groundwater.

Available data for aquatic toxicity are given in the table below. As discussed above, methyl formate is anticipated to differ from the others due to the ester moiety dominating the initial acute toxic effects prior to hydrolysis. Formic acid is anticipated to differ by virtue of its acidity. It can be calculated from the K_a that, without buffering, a 10 mg/L solution of formic acid will have an approximate pH of 3.7 and the expected pH is 3.2 at 100 mg/L. It is apparent from the sodium formate data that the formate ion itself has a low order of toxicity and since calcium ion is known to be of low aquatic toxicity (52) it

is evident that calcium formate will also have low order of toxicity toward these aquatic species.

Material	LC_{50} or EC_{50} (mg/L)		
	Fish	Daphnids	Algae
Formic acid (4)	46-175*	120-150	25
Calcium formate (5)	>1000	NA	NA
Sodium formate (6)	>5000	>1000	~1000
Methyl formate (7)	120	>500	190-240
(Methanol) (53)	>1000	>1000	>1000

* Without pH adjustment, with pH adjustment the LC_{50} is the same as sodium formate.

NA means not available

One concern with the aquatic data is the hydrolysis and volatility of methyl formate. Environmental hydrolysis of methyl formate at pH 7 to 9 is known to be a facile process yielding methanol and formic acid (54). At pH 8 and 25˚ C the hydrolytic half-life of methyl formate in aqueous solution is calculated to be 5.3 hours based on the published K_b. Under typical environmental conditions, formic acid produced by hydrolysis will react with water to give formate ion that will biodegrade to carbon dioxide. The methanol produced by hydrolysis will be biologically oxidized via formaldehyde to formate and finally carbon dioxide. It can be argued that the static toxicity test, where hydrolysis products are allowed to form, is a more realistic test of the acute toxicity of this material in the environment; however, in situations where there is a continuous influx of material in to the environment, a flow through test might be more appropriate relative to a localized area of a waterway. Logically, with the low Ko/w of methyl formate and the high rate of abiotic and biotic hydrolysis, accumulative effects are not anticipated to be important for fish and daphnids and the available static results are considered acceptable for the aquatic toxicity endpoints.

In addition, the EPA ECOSAR model for esters gives a predicted 96-hour LC/EC_{50} of 132 mg/L for fish, 4500 mg/L for daphnids and 9 mg/L for algae. These are in accord with the observed static results. The experimental algae result of an IC_{50} in the range of

190-240 mg/L is easily reconciled. This is the expected apparent result over a 96-hour study if there is an initial strong inhibition of growth followed by rapid hydrolysis of methyl formate to the essentially non-inhibitory methanol and formate. The EPA ECOSAR model does not take hydrolysis into consideration; therefore, the predicted value may be in accord with the experimental value for algal inhibition. Based on the available test results and the known environmental fate of formic acid and methanol, the aquatic hazard of methyl formate is sufficiently characterized for the purposes of the HPV Program.

In summary, the formates as a category have low aquatic hazard with the exception of pH effects of formic acid and an initial moderate toxicity of methyl formate to fish and algae which is followed by a rapid hydrolysis to the less toxic products of methanol and formate.

Summary and Recommendations for Environmental Effects

All environmental effect parameters for all members of the category have adequate information to meet the HPV Program requirements. No testing is recommended.

Health Effects

Acute Oral Toxicity

As with the environmental effects, the acute oral toxicity of formate itself appears to be very low; however, the acidity associated with formic acid appears to increase the acute oral toxicity of this substance and the solvent-narcotic effect of methyl formate appears to increase its acute toxicity.

Formic Acid

Several acute oral toxicity tests of formic acid have been conducted giving LD_{50} values between 730 mg/kg and 1830 mg/kg (55). The lowest LD_{50} value (730 mg/kg) is selected as the key study as it is both the lowest and the study followed the OECD 401 guideline using four dose levels and groups of 5 rats of each sex (56).

Sodium and Calcium Formate

The acute oral LD_{50} for both these materials is high and similar showing the low level of acute toxicity associated with the formate ion. Calcium formate has three studies conducted giving LD_{50} values of 2650, 2560 and 3050 mg/kg (5). According to the IUCLID 2000 document, sodium formate had an OECD 401 guideline study conducted in 1989. The result of this unpublished study is an LD_{50} >3000 mg/kg (57). Neither additional details nor the study report were available for review.

Methyl Formate

The key study for methyl formate acute oral toxicity, giving an LD_{50} of 1500 mg/kg, was conducted in 1979 using five Sprague-Dawley rats of each sex at doses of 464, 681, 1000, 1470, or 2150 mg/kg. All high-dose animals died, 2/5 males and 2/5 females died in the 1470-mg/kg dose groups. Surviving rats gained weight and did not appear to have delayed effects. All deaths occurred within one hour of dosing. The time course of death, clinical observations and post-mortem findings are consistent with solvent-narcotic activity resulting from the bolus dose of methyl formate overwhelming the hydrolytic capability of the test animals, being the cause of death (7).

Summary and Recommendations for Acute Oral Toxicity

For the purposes of the HPV Challenge Program, the acute oral toxicity is sufficiently characterized for all members of the category. No further testing is recommended.

Acute Inhalation Toxicity

Acute inhalation data are available for three of the four materials in this category.

Material	LC_{50}
Formic acid	7.4 mg/L
Calcium formate	No data
Sodium formate	>0.64 mg/L
Methyl formate	>21 mg/L

Formic Acid

The acute inhalation LC_{50} for formic acid is reported as 7.4 mg/L in IUCLID-2000 with the notation that it was a BASF test using 10 animals of each sex per group with a 14-day observation period. No details or report were available for review (58).

Sodium Formate

The acute inhalation toxicity of sodium formate was determined to be > 0.67 mg/L in a 1990 GLP study using the solid aerosol. The study was conducted at what was considered the maximum attainable inhalation concentration. Milled test material was used and a MMAD of 5.4 microns was measured in the chamber. All animals survived the 4-hour exposure and the 14-day observation period. The only adverse effects notes were lacrimation and nasal discharge (59).

Calcium Formate

No inhalation studies were located, based on the sodium formate results and the minimal toxicity of calcium salts, calcium formate can be considered to have low inhalation hazard.

Methyl Formate

The 4-hour inhalation LC_{50} of methyl formate was determined to be > 21 mg/L in a GLP study conducted using measured concentrations of test material (60). The study was conducted using a single concentration level and adverse effects were minimal. This study is described in detail in the robust summaries. Additional supporting studies are also available and are cited in the robust summary (7).

Summary and Recommendations for Acute Inhalation Toxicity

For the purposes of the HPV Challenge Program, the acute inhalation toxicity is sufficiently characterized for all members of the category. No further testing is recommended.

Acute Dermal Toxicity

The acute dermal toxicity of methyl formate in rats was found to be >4000 mg/kg in a 1979 unpublished study (61). Clinical signs including staggering and irregular breathing indicated dermal absorption and sublethal effects at this dose level. This is supported by a 1990 screening-level dermal toxicity study of methyl formate sponsored by Hoechst Celanese in which 0/4 treated rabbits died at a dermal dose of 5,000 mg/kg (62).

No testing is indicated for the other materials since formic acid is corrosive to the skin and the other two materials are salts of materials having low toxicity.

Summary and Recommendations

Acute dermal toxicity information relevant to the HPV Program is known, can be estimated with sufficient confidence, or is irrelevant for all members of the category. No testing is recommended.

Repeated Dose Toxicity

Formic Acid

The National Toxicology Program has conducted 2-week and 13-week inhalation studies with formic acid. The results show little systemic toxicity and the primary adverse effects involve the nasal epithelium. The 13-week NOAEL for rats and mice was reported to be 32 ppm. It was concluded in the abstract of the report: "Overall, the effects of formic acid were consistent with those of irritant chemicals administered by inhalation exposure. The no-observed-adverse-effect level (NOAEL) for respiratory injury was 32 ppm in rats and mice. There was no significant evidence of systemic toxicity in these studies." (20).

A feeding study using pigs was conducted with duration of approximately 90-days examining the effect of feeding Ca/Na-formate (50:50 weight basis) or K-diformate (30% potassium, 35.4 % formic acid and 34.6% formates) at 0, 0.6 or 1.2% of the diet to growing-finishing pigs (63). The K-diformate has previously been shown to be an effective growth promoter in diets of both weaning pigs (64) and growing-finishing pigs (65). There was no effect of the Ca/Na-formate on growth or any other measured parameter. K-diformate, added on top of the basal diet, significantly increased the growth rate of the pigs. There were no adverse effects on the health status of pigs fed K-diformate and an examination of the stomachs at necropsy revealed no effect on stomach keratinization or ulceration. Additional studies revealed that feeding 1.2% K-diformate to pigs decreases the coliform bacteria level in the gastrointestinal tract. The presumed mechanism of action was reportedly partially explained by reduction of the population of gut coliform bacteria leading to reduced metabolic needs of gut bacteria and improved availability of dietary nutrients for the animal.

Sodium Formate

A one-and-a-half-year drinking-water study has been conducted using sodium formate. The results are only available as a brief keynote address and describe a study using six

rats per group exposed to one percent sodium formate in the drinking water for one and a half years. The conclusion was that no toxicity was detected (66). The pig-feeding studies listed under formic acid also contained sodium formate and suggest a lack of toxic effect at moderate dose levels after repeated oral exposure.

Calcium Formate

A lifetime drinking water study has been conducted with calcium formate in the drinking water at 0, 0.2, or 0.4% (150-200 mg/kg/day in the lowest dose according to the authors). Six rats per group were used and the results are only summarized in keynotes or presented briefly in a table in the case of body weight gain. Macroscopic and histological examinations were conducted upon the natural death of the animals. No significant clinical or pathologic changes (growth or organ functions) were detected in any dose group; in particular, there were no disorders of the ocular fundus. The study includes several generations (up to 5). At the beginning, 8 males and 24 females were used (66). A summary of this study may also be found in the IUCLID document for formic acid. The pig-feeding studies listed under formic acid also contained calcium formate and suggest a lack of calcium formate induced toxic effect at moderate dose levels.

Methyl Formate

No data were found for methyl formate; however, information is available for its degradation products methanol and formic acid. Dahl et al. (67) have demonstrated that carboxylesterases are very active in the respiratory tract of rats, rabbits and hamsters. These authors concluded, "The foregoing calculations, based upon the experimental results, indicate that inhaled esters may be largely converted to hydrolysis products in the nasal cavity". Beyond the nasal cavity of rats, these authors found that the rat lung had about half the carboxylesterases activity (on a per mg protein basis) as the nasal epithelium and the liver had about twice the carboxylesterases activity of nasal epithelium. Thus, ample additional esterase activity is available to rapidly hyrdolyse esters that make it past the nasal epithelium. Recently, Niehlen and Droz developed and validated a toxicokinetic model of methyl formate absorption, metabolism and excretion in humans. The first-order rate constant for hydrolysis of methyl formate was estimated by fitting the toxicokinetic model to individual experimental data from 36 methyl formate

exposed individuals. The range of values obtained from these subjects was from 4.3 to 7.3 min^{-1}. The value selected for use in the model is 6.7 min^{-1}, which corresponds to a half-life of 6.1 seconds (11). These studies indicate that the systemic hazard of methyl formate inhalation can be established from the results of methanol and formic acid systemic exposure studies.

In the NTP formic acid studies, discussed under formic acid, there was no evidence of systemic toxicity after inhalation exposure of rats or mice to formic acid vapor up to 500 ppm for 2 weeks (5 days a week, 6 hours a day) or up to 128 ppm for 13 weeks (5 days a week, 6 hours a day).

There are several studies demonstrating the low toxicity of methanol to experimental animals. Exposure of rats to methanol vapor up to 5000 ppm for 4 weeks (5 days a week, 6 hours a day) resulted in only mucoid nasal discharge while monkeys tolerated 5000 ppm under these conditions with only a slight increase in the spleen weight of females (68). Rats exposed to methanol vapor daily for 20 hours a day for up to two years or mice exposed for up to 18 months at 10, 100 or 1000 ppm showed minimal treatment related effects (69). Monkeys exposed to methanol vapor for 21 hours a day in a series of range-finding subacute studies showed no adverse effects at 3000 ppm or below but demonstrated adverse clinical signs at 5000 ppm and above. After daily chronic exposure of up to 7 months for 21 hours a day, 1000 ppm was found to be a LOAEL. In a 30-month inhalation study, monkeys exposed daily for 22 hours a day demonstrated slight liver and kidney effects at 1000 ppm, kidney effects at 100 ppm and CNS effects which were considered transient at 10, 100 and 1000 ppm. (69). Gavage administration of methanol to rats for 90 days at 0, 100, 500 or 2500 mg/kg/day produced few adverse effects. Some organ weights were affected at the high dose without corresponding histopathological changes. The NOEL was 500 mg/kg (70).

In addition to these studies of formic acid and methanol, a recent 4-week study on the close analog methyl acetate has been conducted. In this study, male and female rats were exposed by inhalation to vapors of methyl acetate for 6 hours a day, 5 days a week for 4 weeks at concentrations of 0, 75, 350 or 2000 ppm. The only adverse effect found after this exposure was degeneration of the nasal epithelium in 19/20 treated high-dose rats. The 350-ppm level was considered a NOAEL. Blood levels of methyl acetate were determined immediately upon cessation of the study and no methyl acetate could be

found in the blood of exposed animals. This indicates the experimental animals effectively and rapidly hydrolyzed inhaled methyl acetate (71).

Summary and Recommendations for Repeated Dose Toxicity

Sufficient data are available within this category to meet the requirements of the HPV Challenge Program. Methyl formate has not been directly studied but studies of the other formates, methanol and methyl acetate provide evidence that significant adverse systemic effects from repeated administration of methyl formate are unlikely. The only adverse effect anticipated from methyl formate inhalation exposure at high levels is degeneration of the nasal epithelium. No further testing is recommended.

Genetic Toxicity *In Vitro*

All four materials have been found negative in the Ames test as shown in the table.

Results of Ames Testing on Formates

Material	Result	Guideline Study	Year	GLP	Ref
Formic acid[#]	-/-*		1975, 1983		20, 72, 73
Calcium formate	-/-	Yes	1983	Yes	74
Sodium formate	-/-	No	1975	No	75
Methyl formate	-/-	No	1989	Yes	76

* -/- indicates negative in the presence of absence of liver S9 fraction

\# Formic acid has multiple negative Ames tests

Other *In Vitro* Assays

Formic acid

A published cytogenetic assay using CHO-K1 cells produced ambiguous results for chromosome aberrations. The unbuffered or unneutralized acid was clastogenic at pH

values around 6.0 (10-14 mM) and cytotoxic at and below pH 5.7 (12-16 mM). Clastogenicity is stopped by neutralization with sodium hydroxide or by increasing the buffer concentrations in the incubation medium. The authors conclude from this that it is not the substance as such that induces chromosome damage but that the damage is due to the acid pH of the incubation medium as a nonspecific effect. The study was conducted basically in accord with the OECD 473 guideline "*In Vitro* Mammalian Chromosome Aberration Test" (77).

Two sister chromatid exchange assays have been conducted using formic acid. Both produced negative results. One utilized Chinese hamster V79 cells at formic acid concentrations of 0.4, 0.6, 1.0 and 2.0 mM with and without an activation system (78). The second utilized human lymphocytes at a formic acid concentration from 29 - 460 ug/ml (0.63 - 10 mM) with an activation system (79).

An *E. coli* reverse mutation assay without activation produced slightly positive results. In this 1951 report, the number of bacteria was varied while the test substance concentration remained at almost the same level. The survival rate was reduced with a decrease in the bacterial count (from 100% at 1.5 x 10^9 bacteria up to 2.8% at 2.6 x 10^7). In parallel, the number of mutations was reduced with an increase in the survival rate (80). Other bacterial (Ames) tests produced negative results as indicated above.

Formic acid was reported to be negative in a SOS chromotest. The test was conducted with and without an activation system and used 3-5 concentrations at up to 100 mM (81).

Sodium Formate

A bacteria reverse-mutation assay of sodium formate produced negative results (75). This is consistent with the other formates that were negative in the Ames test.

Sodium formate was tested for clastogenicity by Morita et al. (77) who tested formic acid neutralized with sodium hydroxide or sodium bicarbonate (both of which produce sodium formate) in cultured CHO-K1 cells. This peer-reviewed report describes an OECD 473 like study in which it was demonstrated that sodium formate is not clastogenic to these cells. The study was further strengthened by the demonstration that neither acetic acid nor lactic acid was clastogenic after neutralization to sodium acetate and sodium lactate although they displayed clastogenic activity at acid pH.

Sodium formate was reported positive in a mouse lymphoma assay in both the presence and absence of metabolic activation. The study is reported with no details in the Chemical Carcinogenesis Research Information System file (maintained by the National Library of Medicine) (82); no report has been located describing the conditions of this study. Based on the year of the study (1982 or earlier) and the lack of positive mutagenicity data for other tests and members of this category, this positive result is considered suspicious, as colony sizing was probably not conducted. The current OECD 476 (adopted 21 July 1997) guideline requires colony sizing to confirm the positive result. Likewise, the 1994 Mammalian Cell Gene Mutation Assays Working Group report (83) states that "Ability to recover small colonies must be convincingly demonstrated when using the L5178Y TK mouse lymphoma assay". In addition, the 1995 report by Coombs et al (84) also emphasizes the importance of colony sizing to the acceptability of mouse lymphoma results. Thus, this report is considered unreliable.

Genetic Toxicity *In Vivo*

Formic Acid

A Drosophila SLRL test was performed using oral (feed) or inhalation exposure. The mutation result was positive after inhalation exposure and administration via the diet with mutation rates of 1.31 and 1.11% as compared with the control limit of 0.15% in each case. If the pH was buffered to 7.5 in the feeding study, there was no increased mutation rate. The positive effect was likely due to the pH of the acid form used in the testing (85, 86).

Sodium Formate

Formic acid neutralized with glycine-NaOH buffer was tested in a Drosophila SLRL test using oral exposure. After feeding for the entire larval stage of development, males did not show an increase in mutation rate at 0.1% formic acid neutralized. Feeding the acid form without neutralization produced a statistically significant positive result (86).

Methyl Formate

No studies of methyl formate itself are available; however, as it is known that methyl formate is rapidly hydrolyzed to formic acid and methanol, the data for these compounds is relevant. Formic acid data is provided in this document and the methanol data can be found in the HPV document for methanol (EPA RTK website). Methanol has been extensively studied for potential genotoxicity and the weight of evidence indicates lack of genotoxicity.

Summary and Recommendations for Genetic Toxicology

The genetic toxicology data set for formates suggest a lack of genotoxic potential. Positive results that have been obtained were attributed to low pH values in the test systems as has been reported in the literature for other acids (87). For the purposes of the HPV Program, it is recommended that additional data be obtained for methyl formate. As formate is a naturally constituent of human metabolism and as methanol has been extensively tested, the priority for conducting this testing with live animals is reduced. In addition, the close analog methyl acetate was not genotoxic in a rat micronucleus assay at inhalation doses of up to 2000 ppm (71). It is recommended that rather than using living animals to obtain these data, tissue culture techniques be employed. Thus, the recommendation is for a chromosome aberration study with methyl formate using an appropriate tissue culture system to simulate *in vivo* conditions. This is consistent with the October 14, 1999 letter from EPA to sponsors.

Reproductive Toxicity

Reproductive toxicity studies of formates are limited; however, a multigeneration drinking-water study with calcium formate has been conducted.

Formic Acid

There are data from the 13-week NTP inhalation study covering some reproductive systems that do not indicate any obvious reproductive toxicity.

- In the rat study it is stated that for the SMVCE parameters "There were no effects of exposure to formic acid on measures of sperm motility, density, or testicular or epididymal weights, and no changes were seen in the length of the estrous cycle."
- In the 13-week mouse study, it is concluded "There were no adverse effects of formic acid exposure on reproductive parameters evaluated in male or female mice (Appendix C). Sperm motility was somewhat lower in the exposed groups compared to controls, but the values for controls were rather high, and the values for exposed mice fall well within the historical range for control mice."
- In rats, no histopathological, gross or organ weight changes were noted in male or female reproductive organ systems after 2-weeks of exposure at up to 500 ppm or after 13-week exposure at up to 14-days.
- In mice, no histopathological, gross or organ weight changes were noted in male or female reproductive organ systems after 2-weeks of exposure at up to 500 ppm or after 13-week exposure at up to 14-days.

Calcium Formate

Results of a three-generation drinking water study at 0 or 200 mg/kg/day calcium formate in the drinking water have been published (66). Number, weight and length of offspring did not differ in treated animals from controls. An additional study of identical design at 400 mg/kg/day was stated in the report as producing no adverse effects. In these studies, a portion of the offspring was also sacrificed shortly after birth for evaluation of developmental toxicity. No statistical differences in organ or bone abnormalities were found. The growth of treated offspring was similar to controls. Presentation of data is limited to the 200 mg/kg dose group.

Sodium Formate

No studies were identified except it was stated in the calcium formate multigenerational study publication that a similar study was underway with 1% sodium formate (ca 1000 mg/kg/day). This study was stated to be ongoing for one and a half years and no effects indicating that this treatment was harmful had been observed. Data, however, were not presented and results showing that this study was completed were not found in the open literature (66).

Methyl Formate

No studies of methyl formate were found; however, data on formic acid and methanol are relevant in estimating the reproductive hazard of methyl formate. The formic acid data are discussed above and methanol has been well studied for reproductive toxicity.

There are conflicting reports on the effects of methanol on testicular function. Cameron et al. (88, 89) reported that male rats exposed repeatedly by inhalation (260, 2600 or 13000 mg/m^3) to methanol demonstrated reduced serum levels of testosterone. Cooper et al (90) also reported lowered testosterone levels, decreased testis weight, and decreased numbers of morphologically normal sperm after gavage dosing for 21 days with 1,600 mg/kg/day methanol but not with 800 mg/kg/day.

In contrast to these reports, Lee et al. (91) reported that rats exposed by inhalation to 260 mg/m^3 for up to 6 weeks did not show any changes in serum testosterone, or in testis or seminal vesicle weights, or several *in vitro* biochemical parameters. In addition, normal or folate deficient rats exposed to 1,040 mg/m^3 methanol for 20 hours a day, 7 days a week for up to 13 weeks did not show any effects on testicular morphology, testis weights or seminal vesicle weight. Older folate deficient rats, however, exposed to methanol did have an increased incidence of age-related testicular degeneration.

Summary and Recommendations for Reproductive Toxicity

Limited data are available for formates regarding reproductive toxicity. Low-level exposures are not of concern because formate is a normal component of human metabolism. Higher-level exposure is unlikely to result in significant reproductive toxicity based on the data from formic acid and calcium formate. Methyl formate reproductive toxicity may be defined by any representative formate and the extensive methanol data showing minimal risk from low to moderate methanol exposure. For EPA HPV Program purposes, the present data from subchronic studies with examination of reproductive organs will be considered sufficient for the formate category provided a definitive developmental toxicity is conducted on a representative formate.

Developmental Toxicity

The only *in vivo* developmental toxicity study known for formates is the calcium formate multigenerational study described above in the reproductive toxicity section. In the publication of this study, it was also reported that sodium formate injected into eggs at 5, 10 or 20 mg, had no effect qualitatively or quantitatively on the malformation spectrum of frequency of the resultant chicks (66). Both the rat study and the chicken study showed no evidence of developmental toxicity but are not considered adequate in design or reporting. No definitive studies on developmental toxicity of any of these formates were located.

Studies of methanol developmental toxicity are relevant to the formate category since it is a metabolite of methyl formate and is itself metabolized to formate. Developmental toxicity studies of methanol suggest the potential to cause developmental toxicity in experimental animals. An inhalation study in mice at 1,000, 2,000, 5,000, 7,500, 10,000, or 15,000 ppm methanol for 7 hr/day on days 6-15 of gestation was conducted in which the NOAEL for developmental toxicity was 1000 ppm (92). In this study, methanol doses of 5,000 ppm or higher caused significant increases in the incidence of exencephaly and cleft palate. Doses of 2,000 ppm or higher induced increases in the frequency of cervical rib formation or ossification sites lateral to the seventh cervical vertebra. Maternal toxicity was only reported at 7500 ppm and above. This investigation was extended to examine the effect of methanol exposure at various times during development. It was concluded that the conceptus is most sensitive to the effects of inhaled methanol during gastrulation and early organogenesis (93). Other developmental toxicity investigations have been conducted and provide results that are broadly similar. For example, the inhalation NOAEL for developmental effects in the rat is 5000 ppm (94). The developmental toxicity of methanol was also shown to be exacerbated in mice provided a folic-acid deficient diet (95, 96). This observation indicates that formate, which is oxidized by a tetrahydrofolate pathway, is at least partly responsible for the adverse developmental effects of methanol. It is not known if formate alone can produce the same effects in a standard developmental toxicity study.

The developmental toxicity of formate and formic acid have been investigated using whole embryo culture of rats and mice (97). It was reported that both formic acid and sodium formate are approximately equally embryotoxic and are four to eight times more

potent than methanol at the same molar concentration. In a study designed to elucidate further details on the relationship of formate to methanol developmental toxicity, the combined effect of methanol and formic acid on rat embryos in whole embryo culture was examined (98). The authors concluded that the combined exposure had less effect on the cultured embryos than was predicted by simple additively and therefore the mechanism of activity is likely different for the two agents. This result also demonstrates that the dysmorphogenic effects observed in the presence of methanol are not likely due to a synergistic combined effect of methanol with its metabolite formate.

Gavage administration of sodium formate (750 mg/kg) to pregnant CD-1 mice on gestational day eight did not result in exencephaly in spite of the fact that it produced a peak blood formate level similar to that produced following a 6-hour exposure to 15,000 ppm methanol (99). This observation led the authors to conclude that developmental toxicity of methanol by inhalation in CD-a mice was not a result of the accumulation of formate but a direct result of the methanol concentration.

Overall, the studies conducted using formate to investigate methanol-induced developmental toxicity have been inconclusive and additional information would help provide further understanding of the potential of high doses of formate to cause developmental toxicity.

Summary and Recommendations for Developmental Toxicity

Limited data are available for this category regarding developmental toxicity. Low-level exposures are not of concern because formate is a normal component of human metabolism. Higher-level exposure may be selectively hazardous to the conceptus. A definitive study on a representative formate – such as sodium formate – where the formate dosage may be maximized without causing narcosis or acidosis is recommended as a means of completing HPV Program requirements.

Overall Summary

Relative to the HPV program, most of the requested screening data for this category of chemicals are available or can be reliably estimated. Some of the existing studies are not

of modern quality but data from other members of the class increases the overall confidence of the data sets for fate, environmental effects and acute health effects. The consistency of the available data confirms the validity of grouping these materials into a category.

Although multi-generational studies have been conducted for formate salts without producing developmental effects, the studies are not sufficiently robust to fill the developmental data endpoint. Genetic toxicity data are sufficient for formates as a category; however, the properties of methyl formate differ from the ionic formates sufficiently that genotoxic effects on cells exposed to the ester directly cannot be reliably estimated. In the case of *in vivo* genotoxicity the rapid hydrolysis to methanol and formate acid and the strong data sets for these two materials (and the metabolic conversion of methanol to formate) indicate that *in vivo* genetic toxicity can be reliably predicted. The fact that formates are a normal constituent of human metabolism further reduces the concern of low-level hazard; however, testing of selected materials in these two areas (developmental toxicity and *in vitro* cytogenetics) would add to the confidence of the hazard evaluation for this category.

Recommended testing for the category is an *in vitro* genotoxicity test (OECD 476) for methyl formate and developmental toxicity testing in rats of a representative formate. Sodium formate is recommended as the preferred salt to be tested for developmental toxicity as pH effects and irritation will be minimized, and as sodium is the most common extracellular cation. It is further recommended that a sodium control group be added to account for any role of excess sodium cation on development. In addition to these recommendations, it should be kept in mind that a European consortium is addressing the data-set for formic acid under the ICCA program.

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Robust Summaries Follow as IUCLID Style Documents

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I U C L I D

Data Set

Existing Chemical	:	ID: 141-53-7
CAS No.	:	141-53-7
EINECS Name	:	sodium formate
EINECS No.	:	205-488-0
TSCA Name	:	Formic acid, sodium salt
Molecular Formula	:	CH2O2.Na
Printing date	:	19.12.2001
Revision date	:	
Date of last Update	:	19.12.2001
Number of Pages	:	24
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type : lead organisation
Name : American Chemistry Council, Formates Panel
Partner :
Date :
Street : 1300 Wilson Boulevard
Town : 22209 Arlington, VA
Country : United States
Phone :
Telefax :
Telex :
Cedex :
25.05.2001

Type : cooperating company
Name : BASF Corporation
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
19.12.2001

Type : cooperating company
Name : Bayer Corporation
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
19.12.2001

Type : cooperating company
Name : Celanese Ltd
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
19.12.2001

Type : cooperating company
Name : GEO Specialty Chemicals
Partner :
Date :
Street :

Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
19.12.2001

Type : cooperating company
Name : Hercules Inc
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
19.12.2001

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organometallic
Physical status : solid
Purity : % w/w
Test substance : Varies
19.12.2001

25.05.2001

1.2 SYNONYMS

Ameisensaeure, Natriumsalz
25.05.2001

Formic acid, sodium salt
25.05.2001

Natriumformiat
25.05.2001

Sodium methanoate
25.05.2001

2.1 MELTING POINT

Value	:	= 253 ° C
Sublimation	:	
Method	:	
Year	:	
GLP	:	no
Test substance	:	
Reliability	:	(2) valid with restrictions

25.05.2001 (22)

2.2 BOILING POINT

2.4 VAPOUR PRESSURE

Value	:	= 0 at ° C
Remark	:	This material is a solid salt and as such is considered to have negligible vapor pressure. It should be kept in mind, however, that it is in equilibrium with formic acid in solution and volatilization from solution is therefore pH dependent.
Conclusion		Material considered non-volatile as a dry solid.
Reliability	:	(4) not assignable

13.11.2001 (22)

2.5 PARTITION COEFFICIENT

2.6.1 WATER SOLUBILITY

Value	:	= 550 g/l at 20 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	ca. 9 - 10 at 50 g/l and 20 ° C
Source	:	Huels AG Marl
Reliability	:	(2) valid with restrictions

25.05.2001 (22) (25)

3.1.1 PHOTODEGRADATION

Type	:	other
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Remark	:	Since this material is not volatile, the only potential photolytic reaction that needs to be considered is direct photolysis at the earths surface. Direct photolysis is not possible because this material does not have a chromophore absorbing at a wavelength of 290 nm or above, and the presence of such a chromophore is a necessary condition for photolysis.
Reliability	:	(4) not assignable

14.11.2001 (17)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	at degree C
t1/2 pH9	:	at degree C
Remark	:	Disassociates in water to sodium ion and formate ion. Both of these are considered stable in water. A carboxylic acid is generally the final product of hydrolysis reactions
Reliability	:	(4) not assignable

14.11.2001 (16)

3.3.2 DISTRIBUTION

Media	:	air - biota - sediment(s) - soil - water
Method	:	Calculation according Mackay, Level III
Year	:	2001
Remark	:	Assumptions used in model:

Molecular Wt: 68.01
Henry's LC : 7.53e-007 atm-m3/mole (Henrywin program)
Vapor Press : 7.53e-008 mm Hg (Mpbpwin program)
Liquid VP : 9.87e-007 mm Hg (super-cooled)
Melting Pt : 138 deg C (Mpbpwin program)
Log Kow : -4.27 (Kowwin program)
Soil Koc : 2.2e-005 (calc by model)

Half-Lives (hr), (based upon user-entry)*
Air: 504
Water: 120
Soil: 120
Sediment: 1440

* This calculation was conducted using a water half-life of 120 hours based

on actual data. The soil half-life was estimated at 120 hours on the basis of the water value. Air half-life was set at 504 hours which is the model calculated result for formic acid. This was done presuming that volatilized material would exist primarily as formic acid.

Result :

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	7.11	1e+005	1000
Water	48.7	360	1000
Soil	44.1	360	1000
Sediment	0.0811	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	7.03e-011	51.4	374	1.71	12.5
Water	1.03e-011	1.07e+003	186	35.7	6.19
Soil	4.67e-010	1.32e+003	0	43.9	0
Sed	8.56e-012	0.149	0.00619	0.00496	0.000206

Persistence Time: 150 hr
Reaction Time: 185 hr
Advection Time: 807 hr
Percent Reacted: 81.3
Percent Advected: 18.7

Half-Lives (hr), (based upon user-entry):
Air: 504
Water: 120
Soil: 120
Sediment: 1440

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Advection Time: 1.19e+003 hr
Percent Reacted: 68.8
Percent Advected: 31.2

Test substance : Sodium Formate CAS Number 141-53-7
Reliability : (2) valid with restrictions
19.12.2001 (7)

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 20mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time :
Degradation : = 92 % after 21 day
Result : readily biodegradable

Deg. Product	:	
Method	:	
Year	:	1981
GLP	:	no
Test substance	:	
Method	:	OECD Guide–line 301 E "Ready biodegradability: Modified OECD Screening Test"
Source	:	Huels AG Marl
Test substance	:	Sodium Formate, CAS Number 141-53-7
Reliability	:	(2) valid with restrictions

15.11.2001 (12)

Type	:	aerobic
Inoculum	:	domestic sewage
Concentration	:	300mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	9 day
Degradation	:	= 100 % after 9 day
Result	:	inherently biodegradable
Deg. Product	:	
Method	:	
Year	:	1985
GLP	:	
Test substance	:	
Method	:	OECD Guide–line 302 B "Inherent biodegradability: Modified"
Remark	:	Inoculum: activated sludge, domestic
Source	:	Huels AG Marl
Test substance	:	Sodium Formate, CAS Number 141-53-7
Conclusion	:	inherently biodegradable
Reliability	:	(4) not assignable

19.12.2001 (11)

Type	:	aerobic
Inoculum	:	domestic sewage
Concentration	:	10mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	= 97.5 % after
Result	:	inherently biodegradable
Method	:	OECD Guide–line 303 A "Simulation Test – Aerobic Sewage"
Remark	:	The 97,5 % loss of DOC refers to an average retention time of 3 hours.
Source	:	Huels AG Marl
Test substance	:	Sodium Formate, CAS Number 141-53-7
Reliability	:	(4) not assignable

19.12.2001 (12)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 954
LC0	:	m = 954
LC50	:	c > 1000
Method	:	EPA OTS 797.1400
Year	:	1990
GLP	:	yes
Test substance	:	
Method	:	The study was conducted using a flow-through design at 5 nominal concentrations (63, 125, 250, 500 and 1000 mg/L) test material. Actual concentrations were measured (duplicate) at the beginning and end of the 96-hour exposure period and the means were: 58, 116, 223, 461 and 954 mg/L. Dilution water was blended soft water with a hardness of 40-48 mg/L, alkalinity of 52-56 mg/L, and a pH of 7.4 to 7.5. Twenty fish (mean weight 0.23 g) per concentration were exposed using a flow rate of 6.4 volume replacements per day for the 30-liter aquaria. Fish were observed daily for mortality and compound related sub-lethal effects. Temperature, oxygen levels and pH were measured at 0, 48 and 96 hours.
Result	:	No mortality or sub-lethal effects were observed at any concentration. Oxygen, temperature and pH were within the protocol specified limits. The measure concentrations were similar to the target (nominal) concentrations.
Source	:	Celanese Ltd
Test substance	:	Sodium formate, described as white granules, received from Hoechst Celanese Corporation coded C-01261. Purity not specified.
Conclusion	:	Under these conditions, the LC50, LC0 and NOEC were all greater than 954 mg/L. The LC50 is greater than 1000 mg/L
Reliability	:	(1) valid without restriction

26.05.2001 (3)

Type	:	flow through
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m > 887
LC0	:	m > 887
LC50	:	c > 1000
Method	:	EPA OTS 797.1400
Year	:	1990
GLP	:	yes
Test substance	:	
Method	:	The study was conducted using a flow-through design at 5 nominal concentrations (63, 125, 250, 500 and 1000 mg/L) test material. Actual concentrations were measured (duplicate) at the beginning and end of the 96-hour exposure period and the means were: 54, 105, 215, 443 and 887 mg/L. Dilution water was blended soft water with a hardness of 48 mg/L, alkalinity of 56-58 mg/L, temperature from 12-13

degrees and a pH of 7.7 to 7.8. Twenty fish (mean weight 0.70 g) per concentration were exposed using a flow rate of 6.4 volume replacements per day for the 30-liter aquaria. Fish were observed daily for mortality and compound related sub-lethal effects. Temperature, oxygen levels and pH were measured at 0, 48 and 96 hours.

Result : No mortality or sub-lethal effects were observed at any concentration. Oxygen, temperature and pH were within the protocol specified limits. The measured concentrations were similar to the target (nominal) concentrations.
Source : Celanese Ltd
Test substance : Sodium formate, described as white granules, received from Hoechst Celanese Corporation coded C-01261. Purity not specified.
Conclusion : Under these conditions, the LC50, LC0 and NOEC were all greater than 887 mg/L. The LC50 is greater than 1000 mg/L
Reliability : (1) valid without restriction
26.05.2001 (1)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring :
LC50 : m > 1000
Method :
Year :
GLP : no
Test substance :
Method : other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15 (Determination of the effect of substances contained in water on fish, DIN 38412 part of 15)
Source : Huels AG Marl
Test substance : Sodium Formate, CAS Number 141-53-7
Reliability : (4) not assignable
15.11.2001 (13)

Type : static
Species : Lepomis macrochirus (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
Analytical monitoring :
LC50 : m = 5000
Method :
Year : 1965
GLP :
Test substance :
Method : other: Standard method for the determination of the fish toxicity of pure substances after Freeman
Source : Huels AG Marl
Test substance : Sodium Formate, CAS Number 141-53-7
Reliability : (4) not assignable
Rated as 4 since relies on secondary (IUCLID) reference.
15.11.2001 (9) (10)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : flow through
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)

Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 120
EC0	:	m = 247
EC50	:	m > 1070
Method	:	
Year	:	1990
GLP	:	yes
Test substance	:	
Method	:	The study was conducted using a flow-through design at 5 nominal concentrations (60, 120, 250, 500 and 1000 mg/L) test material. Actual concentrations were measured (duplicate) at the beginning and end of the 96-hour exposure period and the means were: 74, 122, 247, 447 and 1070mg/L. Dilution water was blended well water/RO water with a hardness of 178 mg/L, alkalinity of 210 mg/L, and a pH of 7.8. Twenty first-instar daphnids per concentration were exposed (four replicate chambers of five daphnids at each concentration plus control) using a flow rate of 6.1 volume replacements per day for the 1-liter test chambers containing five daphnids each. Daphnids were observed daily for mortality and compound related sub-lethal effects. Temperature, oxygen levels, pH and test material concentrations were measured at 0 and 48 hours.
Result	:	The mortality and extent of sublethal effects are shown in the table.

		MORTALITY		
Nom. Conc	Meas Conc	24 hr	48 hr	Other Effects
0	0	1	1	none
60	74	1	1	none
120	122	0	0	none
250	247	0	0	very few
599	447	1	1	ffew
1000	1070	1	1	Many

Test substance	:	Sodium formate, described as white granules, received from Hoechst Celanese Corporation coded C-01261. Purity not specified.
Conclusion	:	Under these conditions, the EC50 for daphnids was greater than 1070 mg/L, the NOEC was 122 mg/L.
Reliability	:	(1) valid without restriction

19.12.2001 (2)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 125
EC10	:	c = 99
EC50	:	c = 790
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	
Method	:	Two preliminary toxicity tests were conducted to set concentration levels for the definitive test. In the first

96-hour preliminary test, test concentrations of 1, 10 or 100 mg/L produced growth inhibitions of 0, 18 or 50%, respectively. The second preliminary test was started as a definitive test with triplicate cultures at concentrations of 20, 40, 80, 160 or 320 mg/L. Algal cells counts in this study wer 110, 110, 110, 110 or 86 % of the control population. Thus it was determined that there was an insufficient inhibitory response to define the IC50 and a final definitive test was set up. Algal media was inoculated with 1 million cells of test organism into triplicate 250 ml flasks, closed with a foam plug, containing 100 ml algal growth media. Dilutions of test material in growth media were prepared from a 1000 mg/L stock of test material in growth media. Flasks were incubated and agitated (100 rpm) in random positions for 96 hours under 4300 Lux lighting at 24 degrees C. Cell counts were conducted daily for each test replicate using a hemacytometer and compound microscope. Concentration of test material in the media was determined at the beginning and end of the incubation period and mean concentrations reported. Cell counts for each replicate and controls were subjected to analysis of variance (ANOVA) followed by Dunnett's test accepting p< 0.05 as significant. IC50 values were calculated from a regression plot. Two regression plots were constructed using either the mean cell count or the log of the cell count. The regression equation giving the best fit was used to determine the IC50.
.

Remark : Supported by a 1984 Huels study reported in IUCLID 2000, in which the EC50 for Scenedesmus subspicatus was reported to be greater than or equal to 1000 mg/L.
.

Result : Measured concentrations were very close to nominal concentrations, the concentration at termination was similar to the starting concentration and no loss of test material was apparent. Concentrations above 250 mg/L were inhibitory and the data are shown in the table.

Mean cells counts were as follows:

Nomin Conc	Meas Conc	TIME (hours) 24	48	72	96
0(mg/L)	<5	2.9	12	45	140
63	58.3	2.0	8.2*	40	140
125	121	1.1*	8.3*	30*	110
250	243	1.3*	6.8*	28*	93*
500	498	0.78*	4.6*	27*	88*
1000	1001	0.93*	3.5*	8*	61*

Counts are in units of 10,000 cells/ml
* Denotes significant inhibition at p<0.0

A quadratic equation was developed using percent difference in cell count from control versus ln concentration. From this equation, the EC50 was calculated to be 790 mg/L and the EC10 as 99 mg/L (based on nominal concentrations). The NOEC is considered to be 125 mg/L.

Test substance : Sodium formate, described as white granules, received from Hoechst Celanese Corporation coded C-01261. Purity not specified.

Conclusion : Under these conditions, the 96-hour EC50 for algal growth was 790 mg/L and the NOEC was estimated to be 125 mg/L. The

EC10 was calculated to be 99 mg/L from thje regression equation.

Reliability : (1) valid without restriction
15.11.2001 (4)

4.7 BIOLOGICAL EFFECTS MONITORING

Method : Transport Canada conducted and environmental assessment to compare the use of sodium formate (NaFo) with urea as a runway anti-icer/deicer at the Halifax International Airport. Over the winter of 1991-92, 16 tons of NaFo were used on a taxiway with a unique drainage system so that potential environmental effects of NaFo could be identified. Urea was used on two runways and its effects wre compared with those from NAFo. Streams and groundwater were monitored for several parameters with the following issues of primary importance:

* The effect on ground and surface water, especially oxygen depletion
* The effect on the microbial community
* The effect on aquatic biota
* The mobilization of metals
* The effect on vegetation

The effects of sodium formate on surface vegetation growth were also determined in a greenhouse study in which sodium formate solution was applied bi-weekly to representative plants at rates from 0.1 to 48 grams per square meter of soil. Biweekly concentrations at and above 33 g/m2 reduced plant biomass growth. These inhibitory concentrations are, however, very high concentrations that would not be encountered in this application of sodium formate.

Remark : Year 1992

Conclusion : The effects of sodium formate on surface vegetation growth were also determined in a greenhouse study in which sodium formate solution was applied bi-weekly to representative plants at rates from 0.1 to 48 grams per square meter of soil. Biweekly concentrations at and above 33 g/m2 reduced plant biomass growth. These inhibitory concentrations are, however, very high concentrations that would not be encountered in this application of sodium formate.

The conclusions drawn are: The use of sodium formate as a de-icing agent applied during the winter of 1991-1992 at the Halifax international airport, appears to have had no effect on.

1. The in situ concentration of total heterotrophic bacteria whether these were either aerobic or anerobic and either psychrophilic of mesophilic bacteria.
2. The in situ concentrations of fungi, whether these fungi were either psychrophilic or mesophilic moulds.
3. The soil respiration characteristics of the rate of carbon dioxide evolved, the proportion of organic carbon metabolized, or the temperature coefficient Q10.
4. Application of NaFo to vegetated soil from the NaFo test area when applied biweekly at concentrations of less than 2000 mg NaFo/L did not appear to inhibit vegetative plant growth. Application of NaFo at greater concentrations, specifically 3500 and 5000 mg NaFo/L did inhibit vegetative plant growth appreciably (approximately 65 percent and 70 percent respectively).
5. When NaFo was applied in single applications, the inhibition of surface vegetative growth was directly proportional to the mass of NaFo applied. Application of 500 mg NaFo/kg, which is equivalent to 84.5 g/m2 ,

caused 50 percent inhibition. Concentrations of between 1000 and 3500 mg/kg (169 and 591.5 g/M2 respectively) caused approximately 75 percent inhibition and 5000 mg/kg (845 g/m2) caused approximately 95 percent inhibition.
6. Results of the microbiological evaluation tests suggest that, except.at unusually high concentrations of NaFo that are unlikely to be encountered during normal use as a de?icing agent, NaFo causes no deleterious disruptions in the in situ microbiological populations.

Results of the vegetative surface growth tests suggest that when NaFo is applied in moderate concentrations over a prolonged period of time at concentrations of less than 2000 mg NaFo/1, no deleterious disruptions in the plant life may be expected. However, spills of solid NaFo on vegetated surfaces should be avoided, as doses of as little as 1.69 g NaFo/M2 may cause deleterious disruptions in the surface plant growth.

Reliability : (1) valid without restriction
15.11.2001 (26)

13.09.2001

Method :
Conclusion : The conclusions drawn are: The use of sodium formate as a de-icing agent applied during the winter of 1991-1992 at the Halifax international airport, appears to have had no effect on.
1. The in situ concentration of total heterotrophic bacteria whether these were either aerobic or anerobic and either psychrophilic of mesophilic bacteria.
2. The in situ concentrations of fungi, whether these fungi were either psychrophilic or mesophilic moulds.
3. The soil respiration characteristics of the rate of carbon dioxide evolved, the proportion of organic carbon metabolized, or the temperature coefficient Q10.
4. Application of NaFo to vegetated soil from the NaFo test area when applied bi?weekly at concentrations of less than 2000 mg NaFo/L did not appear to inhibit vegetative plant growth. Application of NaFo at greater concentrations, specifically 3500 and 5000 mg NaFo/L did inhibit vegetative plant growth appreciably (approximately 65 percent and 70 percent respectively).
5. When NaFo was applied in single applications, the inhibition of surface vegetative growth was directly proportional to the mass of NaFo applied. Application of 500 mg NaFo/kg, which is equivalent to 84.5 g/m2 , caused 50 percent inhibition. Concentrations of between 1000 and 3500 mg/kg (169 and 591.5 g/M2 respectively) caused approximately 75 percent inhibition and 5000 mg/kg (845 g/m2) caused approximately 95 percent inhibition.
6. Results of the microbiological evaluation tests suggest that, except.at unusually high concentrations of NaFo that are unlikely to be encountered during normal use as a de?icing agent, NaFo causes no deleterious disruptions in the in situ microbiological populations.

13.09.2001

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 3000 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1989
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Information obtained from the IUCLID 2000 document. This is listed as an unpublished study by Hules dated 1989. The full report was not available for review.
Source	:	Huels AG Marl
Test substance	:	Sodium Formate, CAS Number 141-53-7
Reliability	:	(4) not assignable Assigned as 4 since it relies on a secondary source (IUCLID 2000)

15.11.2001 (15)

Type	:	LD50
Species	:	mouse
Strain	:	C57BL
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 4700 mg/kg bw
Method	:	
Year	:	1982
GLP	:	no data
Test substance	:	
Remark	:	C57BL/6Cs folic acid deficient (FAD) mice were used in this study. 12 weeks prior to LD50 determination, 6 mice were fed a diet supplemented with 3 mg of folic acid/kg diet. 6 mice received a diet without folic acid supplements. FAD–mice fed with a supplemented diet showed a slightly higher LD50 (4700 mg/kg) than mice fed a diet without folic acid supplements (LD50 3700 mg/kg).
Source	:	Huels AG Marl
Test substance	:	Sodium Formate, CAS Number 141-53-7
Reliability	:	(2) valid with restrictions

15.11.2001 (23)

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 11200 mg/kg bw
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	
Method	:	Details not provided except that it was part of a series of studies of formic acid and four formate salts and that 54 animals were used to determint the

LD50.

Result :

The LD50 range for sodium formate was given as 9,600 to 12,800

Source : Huels G AG, Literature

Test substance :

Sodium Formate, CAS Number 141-53-7

Reliability : (2) valid with restrictions

Assigned as 2 since it was published with the acute toxicity of several other formates and it fits the expected pattern.

19.12.2001 (19)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC0
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals :
Vehicle :
Exposure time : 4 hour(s)
Value : > .67 mg/l
Method : other
Year : 1990
GLP : yes
Test substance :
Method : The solid test material was milled to a fine powder and placed in a glass fluidizing bed. The material was aerosolized using a flow of 30 liters per minute and the dust from the bed was swept at a rate of 5 L/min into a 100 liter plexiglass exposure chamber. The flow rate was 35 L/min, providing an air change every 2.9 minutes. This was considered the maximum level of dust practically attainable with the equipment. It was determined gravimetrically to contain 0.67 mg/L (nominal concentration based on material loss was 10 mg/L) and have a MMAD of 5.4 microns with an Average Geometric Standard Deviation of 2.4. This aerosol was considered respirable. Five animals (males, 9 weeks of age, weight range 321-344 g; females 10 weeks of age, weight range 223-254 g) of each sex were exposed for 4 hours. Animals remained in the chamber for 30 minutes after the test material was cleared from the breathing air. Animals were doubly housed during the acclimation and post-exposure 14-day observation period and singly housed during the exposure. Animals were observed at 0, 15, 30, 45, 60, 120, 180 and 240 minutes during the 4-hour exposure, then examined daily for 14 days. Surviving animals were sacrificed after 14 days and submitted to a gross necropsy. The chamber temperature was 25 degrees and the relative humidity ranges for 17% to 6% with the lower values in the latter part of the study (considered a result of the dessicant activity of fine particles of sodium formate) Chamber concentration of test material was measured at nine intervals during the study and ranged from 0.5 to 0.86 mg/L.

Result : There were no deaths during the exposure or the 14-day observation period. Adverse clinical sighs were minimal and consisted of decreased activity and eyes partly or fully closed during the exposure and lacrimation and nasal discharge but generally fully recovered within a week. There was a slight and transient reduction in body weight gain (or

weight loss) following the exposure but all animals continued to gain weight a few days after the exposure period:

MEAN BODY WEIGHTS (grams) Exposure 0.67 mg/L (4 hours)

DAY	MALES	FEMALES
1	337	235
2	333	230
5	344	236
8	365	244
15	414	255

There were no treatment-related findings at gross necropsy.

Source : Celanese Ltd

Test condition : C-1261 (Sodium Formate), purity 99% active ingredient. The test material was milled by Sturtevant Inc (Boston) on 8 November 1989 and then sent to BioDynamics.

Conclusion : Exposure of rats to the highest practical aerosol concentration of test material, with a large portion in the respirable range, was not associated with adverse effect other than eye and nasal irritation. The acute inhalation LC50 is greater than 0.67 mg/L for a four-hour inhalation exposure.

15.11.2001 (6)

5.4 REPEATED DOSE TOXICITY

Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : drinking water
Exposure period : Lifetime
Frequency of treatment : Continuous
Post obs. period :
Doses : 1.0%
Control group :
Method :
Year :
GLP : no
Test substance :
Method :

The study design encompassed both a five-generation and chronic study in Wistar rats with sodium formate at 1.0% in drinking water. Eight males and 24 females were in the original test group with four controls of each sex. Both microscopic and pathologic investigations were to be done upon natural death of the animals. At the time of this report the study had completed 1.5 years. Studies with calcium formate had been completed and were reported.

Remark :

Almost no specific details were given of the results of the 1% sodium formate multigeneration study. The indication in the summary was that adverse effects were not observed in the ongoing sodium formate drinking-

water study. Due to the lack of details it cannot be confirmed that this was actually the case. In addition the pathological evaluation of the animals had not been conducted.

A group of dogs was also administered 5 grams sodium formate per day in food. Adverse effects were not reported except that some of the dogs refused to eat the dosed food after a few days.

Result :

Specific results for the sodium formate portion of these rat chronic studies were not given except in the summary where it was mentioned that formate levels up to 1 gram per kilogram per day (the approximate dose level of the sodium formate study) were not harmful to health. Update results for these studies could not be found in the open literature.

Test substance :

Sodium Formate, CAS Number 141-53-7

Conclusion :

Sodium formate at 1% in the drinking water did not produce clinically adverse effects in rats after administration for approximately 18 months. The NOEL cannot be determined since pathological investigations had not been conducted.

Reliability : (4) not assignable
18.11.2001 (18)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Salmonella typhimurium reverse mutation assay
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA1538
Concentration : up to 5000 ug test substance/plate
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other: according to Ames, B.N. et al., Mutat. Res. 31, 347-364
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions
21.09.2001 (14)

Type : Chromosomal aberration test
System of testing : CHO-K1 cells
Concentration : 270, 360, 450, 540, 630 ug/ml (6-14 mM)
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method :
Year :
GLP :
Test substance :
Method :

The study was conducted basically in accord with the OECD 473 guideline "In Vitro Mammalian Chromosome Aberration Test". The only significant variation from this guideline was there were no positive controls reported. As the test materials produced positive results at acidic pH levels, the sensitivity of the procedure was demonstrated.

The procedure was to expose the cells in Ham's F12 medium (with 10% fetal calf serum) to various concentrations of test material for 24 hours in the presence or absence of rat-live S9 prepared from rats pretreated with phenobarbital and 5,6-benzoflavone. At the end of the exposure period, chromosome preparations were made using an air-drying method. Two

hundred metaphases were evaluated per concentration level. Cytotoxicity was assessed by counting surviving cells at the end of the exposure period.

Initially cells were exposed to four concentrations of formic acid in the presence or absence of S9 and evaluated for aberrant cells. These results and the design and results of other studies are provided in "results".

Remark :

This study appears to be a well conducted investigation of the effect of pH on clastogenicity in general and specifically a study of the clastogenicity of formic acid, acetic acid, lactic acid and the sodium salt of these three acids. The procedure closely followed OEDC guideline 473 and the results were published in a peer-reviewed journal. The reliability is further enhanced by the similar results on all three acids and the methodical approach to the problem and conduct of the studies.

Result :

The following dose related increase in aberrant cells was reported:

Conc (mM)	% Aberrant cells	
	(-S9)	(+S9)
6	-	1.0
8	2.0	2.0
10	4.0	20.5
12	15.9	toxic
14	toxic	-

In a second set of experiments the initial pH of the medium was adjusted to pH 5.8 or 6.0 with 14 or 12 mM formic acid it the absence or presence of S9 mix, respectively. These media were then neutralized with 1 M NaOH to pH 6.4 and a second group to pH 7.2. Results were as follows (cell data were read from a graph and are approximate)

Activation	%Aberrant cells		
	pH6.0	pH6.4	pH7.2
-S9	12	4	0
+S9	33	2	3

In a third set of studies, the concentration of the buffer system was increased by supplementation with 34 mM sodium bicarbonate in the absence of S9. Under these conditions, there was no clastogenic activity of 10 or 20 mM formic acid; however, at 25mM 12% aberrant cells were reported and at 30 mM the formic acid was cytotoxic. The 25 and 30 mM concentrations also resulted in acidic pH levels.

Similar studies were also conduced with acetic acid and lactic acid with the same results.

.

Test substance : Sodium formate produced by the neutralization of formic acid with sodium hydroxide or sodium bicarbonate.

Conclusion :

It was concluded that formic acid it not itself clastogenic to these cells but that the acidic conditions were responsible for the chromosome aberrations observed. It can be further concluded the sodium formate (the product of neutralization of formic acid with sodium hydroxide or sodium bicarbonate) is not clastogenic.

Reliability : (1) valid without restriction

16.11.2001 (20)

Type	:	Mouse lymphoma assay
System of testing	:	mouse lymphoma cell line L5178Y TK+/–
Concentration	:	Dose range: 4857-8714 mg/l with metabolic activation; 3571-10000 mg/l without metabolic activation.
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	positive
Method	:	
Year	:	
GLP	:	
Test substance	:	
Remark	:	This positive result is considered suspicious as no colony sizing data were given. The current OECD 476 (adopted 21 July 1977) guideline requires colony sizing to confirm the positive result. Likewise, the 1994 Mammalian cell gene mutation assays working group report (Mutat Res 1994 Jun;312(3):235-9) states that "Ability to recover small colonies must be convincingly demonstrated when using the L5178Y TK mouse lymphoma assay". In addition, the 1997 report by Coombs et al (The use of L5178Y mouse lymphoma cells to assess the mutagenic, clastogenic and aneugenic properties of chemicals. Mutagenesis 1995 Sep;10(5):403-8) also emphasizes the importance of colony sizing to the acceptability of mouse lymphoma results.
Conclusion	:	No firm conclusion about the mutagenic potential can be drawn from this test
Reliability	:	(3) invalid

15.11.2001 (8)

5.6 GENETIC TOXICITY 'IN VITRO'

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	male
Strain	:	other: Oregon-K
Route of admin.	:	oral feed
Exposure period	:	entire larval stage
Doses	:	0.1% as formic acid
Result	:	negative
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	
Method	:	Oregon-K strain of Drosophila melanogaster were treated using dosed feed with 0.1 % formic acid, or sodium formate produced by neutralization of 0.1% formic acid with glycine-NaOH buffer. The Mueller-5 technique was used to determine sex-linked lethals (M Demerec, Induction of mutations in Drosophila by debenzanthracene, Genetics 33:337-48, 1948). About 50 treated males were mated with M-5 virgins and every third day the males were transferred to two fresh virgins in order to produce three successive broods. .
Remark	:	This study was similar in conduct to the current OECD 477 guideline regarding basic methodology; however, it is not clear that higher levels of sodium formate could not have been used to provide a more robust test of sodium formate genotoxicity. .
Result	:	Oregon-K strain of Drosophila melanogaster were treated using dosed feed with 0.1 % formic acid, or sodium formate produced by neutralization of 0.1% formic acid with glycine-NaOH buffer. The Mueller-5 technique was

used to determine sex-linked lethals (M Demerec, Induction of mutations in Drosophila by debenzanthracene, Genetics 33:337-48, 1948). About 50 treated males were mated with M-5 virgins and every third day the males were transferred to two fresh virgins in order to produce three successive broods.
.

After feeding formic acid or sodium formate over the entire larval stage, treated males mated with females gave the following results:

Formic acid

Brood	# Chromosomes Tested	% Sex-linked lethals
1	786	1.15
2	522	1.34
3	571	1.11

Sodium Formate (only one brood tested)

Brood	# Chromosomes Tested	% Sex-linked lethals
2	544	0.38

Controls

Brood	# Chromosomes Tested	% Sex-linked lethals
all	2584	0.15

The sodium formate sex-linked lethal was not different from the control while the formic acid results were stated as bring significantly different from control as determined by the rank-correlation method.

Test substance :

Sodium formate produced by neutralization of 0.1% formic acid with glycine-NaOH buffer.

Conclusion :

Sodium formate produced by neutralization of formic acid is not positive in the Drosophila SLRL test under these conditions; formic acid, at the same molar concentration produced positive results.
.

Reliability : (2) valid with restrictions
15.11.2001 (24)

5.8 TOXICITY TO REPRODUCTION

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	
Strain	:	Sprague-Dawley
Route of admin.	:	other: In vitro incubation using whole-embryo culture
Exposure period	:	48 hr
Frequency of treatment	:	
Duration of test	:	48 hrs
Doses	:	200, 400, 800, 1200, 1600 ug/ml
Control group	:	
Method	:	other: In vitro, whole embryo culture

Year	:	1993
GLP	:	no
Test substance	:	
Remark	:	Other in vitro studies of sodium formate and formic acid on developing embryos have been published and are includid in the formic acid IUCLID document. This study was selected as representative. High concentrations of sodium formate have effects on the embryo in vitro. The significance of this to in vivo developmental toxicity after exposure to formate is not known.
Result	:	The effect of the pH (8.13, 7.75, 7.00, 6.50 and 6.00) on the in vitro teratogenicity of sodium formate (0.2, 0.4, 0.8, 1.2 and 1.6 mg/ml) was investigated in rat embryo cultures (Sprague-Dawley rats, day 9.5 of gestation). Numerous embryonic developmental parameters showed that even the decreasing pH had an influence on embryonic development in this test system. In the highest concentration, the parameters crown-rump length (CRL), head length (HL), somite number (SN), developmental score (DS) and protein concentration were significantly reduced in the incubation medium regardless of the pH. At a test substance concentration of 0.8 and 1.2 mg/ml, these parameters were significantly reduced at a low pH. At a test substance concentration of 0.4 and 0.2 mg/ml, CRL, HL and the protein concentration were still significantly reduced at a pH of 6.5 in the medium. To sum up, a dependence of the embryonic developmental parameters and of embryolethality both on the formate concentration and on the pH in the incubation medium was demonstrated in this test system.
Test substance	:	Sodium Formate, CAS Number 141-53-7
Reliability	:	(2) valid with restrictions
18.11.2001		(5)

Species	:	hen
Sex	:	
Strain	:	
Route of admin.	:	other
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	5 mg, 10 mg or 20 mg/egg
Control group	:	other: negative and positive (0.025 mg hydrocortisone /egg)
Method	:	Sodium formate at 5, 10 or 20 mg/Egg was injected into fertilized eggs.
Result	:	Sodium formate did not cause deviations in chicken embryos under these conditions.
Conclusion	:	Sodium formate was not teratogenic under these conditions
Reliability	:	(2) valid with restrictions
18.11.2001		(18)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Memo	:	Experimental exposure to methylformate and its neurobehavioral effects.
Method	:	Groups of 20 subjects were exposed to 100 ppm methyl formate vapor or air (controls) for eight hours. At three periods during the exposure measurements were taken of mood, neurobehavioral performance, vision, and postural sway. At the beginning and end of exposure, spirometry and

odor perception thresholds were measured.
.

Result : After exposure the subjective feeling of fatigue was significantly increased in the methyl formate exposed group. The EMG of the forehead during a difficult task showed a different development for the exposed group. Overall, there was a tendency for diminished performance on several tasks in the exposed group but it was not significant.
.

Conclusion : Methyl formate exposure at 100 ppm was associated with increased subjective fatigue, no other significant changes were found in battery of tests including mood, neurobehavioral performance, vision, and postural sway.
.

Reliability : (2) valid with restrictions
15.11.2001 (21)

(1) Analytical Biochemistry Laboratories Inc Acute Floe-Through Toxicity of Sodium Formate to Rainbow Trout (Oncorhynchus mykiss. Report #38312, Sponsored by Hoechst Celanese, March 16, 1990.

(2) Analytical Biochemistry Laboratories Inc, Columbia MO. Report #38314 Acute Flow-Through Toxicity of Sodium Formate (C-1261) to Daphnia magna. Hoechst-Celanese sponsor, March 13, 1990

(3) Analytical Biochemistry Laboratories Inc. Acute Flow-Through Toxicity of Sodium Formate to Fathead Minnow (Pimephales promelas). Report #38313, Sponsored by Hoechst Celanese, March 16, 1990.

(4) Analytical Biochemistry Laboratories Inc., Acute Toxicity of Sodium Formate to Selenastrum capricornutum Printz. Report #38315, Sponsored by Hoechst Celanese, March 16, 1990.

(5) Andrews JE; Ebron-McCoy M; Kavlock RJ; Rogers JM. Lowering pH increases embryonic sensitivity to formate in whole embryo culture. Toxicology In Vitro 7:757-62 (1993)

(6) BioDynamics Inc. An Acute Inhalationn Toxicity Study of c-1261 in the Rat. Project # 89-8232, Sponsored by Hoechst Celanese Corp , May 31 1990.

(7) Calculated using the Level III model contained in WPIWIN 3.05 Syracuse Research Corporation 2001.

(8) Cameron, T.P.: Short–Term Test Program sponsored by the devision of cancer etiology, National Cancer Institute: zitiert in CCRIS, Chemical Cancer Research Information System (1991)

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(10) Freeman, L. (1953): Sewage and Industrial Wastes 25, 845-848

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(12) Huels investigation (unpublished) as cited in IUDLID 2000

(13) Huels investigation (unpublished), as cited in IUDLID 2000.

(14) Huels Report No. 88/210 (unpublished)

(15) Hules Report #1579, 1989, unpublished data (as cited in IUCLID 2000)

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(20) Morita, T. et al. Evlauation of clastogenicity of formic acid, acetic acid and lactic acid on cultured mammalian cells Mut. Res. 240, 195-202 (1990)

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(23) Smith, E.N., Taylor, R.T. (1982): Toxicology 25, 271-287 (as cited in IUCLID 2000)

(24) Stumm-Tegethoff, B.F.A.: Theor. Appl. Genetics 39, 330-334 (1969)

(25) Supported by Merck Index listing of "soluble in about 1.3 parts water and Handbook of Chemistry and Physics Listing of v. sol.

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I U C L I D

Data Set

Existing Chemical	:	ID: 544-17-2
CAS No.	:	544-17-2
EINECS Name	:	calcium diformate
EINECS No.	:	208-863-7
TSCA Name	:	Formic acid, calcium salt
Molecular Formula	:	CH2O2.1/2Ca

Printing date	:	20.12.2001
Revision date	:	
Date of last Update	:	20.12.2001

1.0.1 OECD AND COMPANY INFORMATION

Type	:	lead organisation
Name	:	American Chemistry Council, Formates Panel
Partner	:	
Date	:	
Street	:	1300 Wilson Boulevard
Town	:	22209 Arlington, VA
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	

06.12.2000

Type	:	cooperating company
Name	:	BASF Corporation
Partner	:	
Date	:	
Street	:	
Town	:	
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	

Source : Bayer Corporation Pittsburgh
19.12.2001

Type : cooperating company
Name : Bayer Corporation
Partner :
Date :
Street : 100 Bayer Road
Town : 15205-9741 Pittsburgh, PA
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Source :
06.12.2000

Type : cooperating company
Name : Celanese Ltd
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Source :
19.12.2001

Type : cooperating company
Name : GEO Specialty Chemicals
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
19.12.2001

Type : cooperating company
Name : Hercules Incorporated
Partner :
Date :
Street : 1313 North Market Street
Town : 19894-001 Wilmington, DE
Country :
Phone :
Telefax :
Telex :
Cedex :
Source :
06.12.2000

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organometallic
Physical status : solid
Purity : % w/w
Remark : Typical purity > 98%. Purity of material used in the studies varies depending on the source.

20.12.2001

1.2 SYNONYMS

Calcium formate
Source : Bayer Corporation Pittsburgh
Flag : Critical study for SIDS endpoint
05.11.2001

Formic acid, calcium salt
Source : Bayer Corporation Pittsburgh
05.11.2001

2.1 MELTING POINT

Value	:	> 300 ° C
Sublimation	:	
Method	:	other: Handbook value
Year	:	
GLP	:	
Test substance	:	
Source	:	Bayer Corporation Pittsburgh
Reliability	:	(2) valid with restrictions

11.12.2000 (13)

Value	:	>= 800 ° C
Decomposition	:	yes at ° C
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh

11.12.2000 (1)

2.2 BOILING POINT

Remark	:	n.a.

20.12.2001

2.3 DENSITY

Type	:	relative density
Value	:	2.02 at 19° C
Method	:	other: Handbook value
Year	:	
GLP	:	
Test substance	:	
Source	:	Bayer Corporation Pittsburgh
Reliability	:	(2) valid with restrictions

16.11.2001 (14)

Type	:	bulk density
Value	:	1150 kg/m3 at ° C
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh

11.12.2000 (1)

2.4 VAPOUR PRESSURE

Remark	:	This material is a solid salt and as such is considered to have negligible vapor pressure. It should be kept in mind, however, that it is in equilibrium with formic acid in solution and volatilization from solution is therefore pH dependent
Conclusion		Material considered to be non-volatile as a dry solid.

20.12.2001

2.5 PARTITION COEFFICIENT

Log pow	:	-2.47 at ° C
Method		other (calculated):KOWWIN (v1.65)
Year	:	1999
GLP	:	no
Test substance	:	
Remark	:	n.a. (salt) This value is also pH dependent due to equlibrium with formic acid which has a log Kow of about -0.50
Source	:	
Reliability	:	(2) valid with restrictions

20.12.2001 (1)

2.6.1 WATER SOLUBILITY

Value	:	160 g/l at 20 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(4) not assignable

16.11.2001 (1)

Remark	:	Listed in the Merch Index as "Soluble in water"
Reliability	:	(2) valid with restrictions

16.11.2001 (14)

Value	:	ca. 255 g/l at 25 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	Estimation using EPIWIN 3.05 with default inputs
Remark	:	There will be a pH dependency on the Calcium solubility. At basic pH levels the calcium is expected to partially precipitate from solution as calcium hydroxide.
Result	:	Water solubility estimated at 1.96 moles per liter. Based on a molecular weight of 130 this is 255 g/L.
Test substance	:	Calcium Formate, CAS Number 544-17-2
Reliability	:	(2) valid with restrictions

16.11.2001 (7)

2.12 ADDITIONAL REMARKS

Remark	:	pH value: ca. 8 at 1 g/l water
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh

28.05.1994 (1)

3.1.1 PHOTODEGRADATION

Type : other
Rel. intensity : based on Intensity of Sunlight
Remark : Since this material is not volatile, the only potential photolytic reaction that needs to be considered is direct photolysis at the earths surface. Direct photolysis is not possible because this material does not have a chromophore absorbing at a wavelength of 290 nm or above, and the presence of such a chromophore is a necessary condition for photolysis.
Reliability : (4) not assignable
14.11.2001 (9)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at degree C
t1/2 pH7 : at degree C
t1/2 pH9 : at degree C
Remark : Disassociates in water to clacium ion and formate ion. Both of these are considered stable in water. A carboxylic acid is generally the final product of hydrolysis reactions.
Reliability : (4) not assignable
14.11.2001 (9)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level III
Year : 1999
Remark : PROPERTIES OF: Calcium formate

Molecular weight: 130.11
Aqueous solub (mg/l): 1E+006
Vapour pressure (Pa): 3.41305
(atm) 3.36842E-005
(mm Hg) 0.0256
Henry 's law c (Atm-m3/mol): 4.38264E-009
Air-water partition coef: 1.79237E-007
Octanol-water part coef(Kow): 0.00338844
Log Kow: -2.47

Biomass:water part coef: 0.800678
Temperature [deg C] 25

Biodeg rate c(h^-1),T1/2 biomass (h), in 2000 mg/L MLSS (h)
-Primary tank 0.04 15.99 10000.00
-Aeration tank 0.04 15.99 10000.00
-Settling tank 0.04 15.99 10000.00

Result :

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.141	1e+005	1000
Water	45.4	360	1000
Soil	54.4	360	1000
Sed	0.0757	1.44e+003	0

	Fugacity (atm)	Reaction (percent)	Advection (percent)
Air	3.31e-012	0.000408	0.588
Water	9.6e-014	6.6	19
Soil	4.26e-012	43.8	0
Sed	8e-014	0.0152	0.000633

Persistence Time: 419 hr
Reaction Time: 521 hr
Advection Time: 2.14e+003 hr
Percent Reacted: 80.4
Percent Advected: 19.6

Half-Lives (hr), (Biowin (Ultimate) and Aopwin):
Air: 1e+005
Water: 360
Soil: 360
Sediment: 1440
-Biowin estimate: 2.912 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment 1440

Reliability : (2) valid with restrictions
20.12.2001 (12)

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	predominantly domestic sewage
Contact time	:	
Degradation	:	> 75 % after 20 day
Result	:	
Deg. Product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1974
GLP	:	no
Test substance	:	
Remark	:	test concentration: 24 mg/l related to TS
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Test substance	:	Sodium Formate, CAS Number 141-53-7
Reliability	:	(4) not assignable Assigned score of 4 (not assignable) since not enough information was available to evaluate the adequacy of this study.

16.11.2001 (1)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC0	:	>= 1000
Method	:	other: Letale Wirkung beim Zebrabaerbling, UBA-Verfahrensvorschlag, Mai 1984, Letale Wirkung beim Zebrabaerbling Brachydanio rerio LC0, LC50, LC100, 48-96h
Year	:	1988
GLP	:	no
Test substance	:	other TS: calcium formate: technical grade
Method	:	Translation: Lethal effect with the Zebra barbling, UBA suggested procedure, May 1984, lethal effect with the Zebra barbling Brachydanio rerio LC0, LC50, LC100, 48-96h
Result	:	10 Zebrafish were tested at each of the following concentrations: 12.5, 100, 1000 mg/l. There was no mortality at any concentration. The parameters were checked every 24 hrs.
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Test condition	:	Dechlorinated tap water Water hardness: approx. 15 degrees dh Ca: Mg: 4:1 Acid capacity Ks 4.3: 0.1 ±0.02 mmol/l pH: 6.3-6.8 Oxygen saturation greater than or equal to 90%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

16.11.2001 (3)

Type	:	other
Species	:	
Exposure period	:	96 hour(s)
Unit	:	g/l
Analytical monitoring	:	
LC50	:	= 1540
Method	:	other: Calculated (ECOSAR Program) (v0.99e)
Year	:	1999
GLP	:	no
Test substance	:	other TS: molecular structure
Remark	:	The LC50 value is greater than the water solubility (160 g/l).
Source	:	Bayer Corporation Pittsburgh
Test substance	:	Calcium Formate, CAS Number 544-17-2
Reliability	:	(2) valid with restrictions

16.11.2001 (12)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no

LC0	:	>= 1000
Method	:	other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Arbeitskreis "Fischtest" im Hauptausschuss "Detergentien" (15.10.73)
Year	:	1974
GLP	:	no
Test substance	:	
Method	:	Translation: Determination of the acute effect of materials on fish. Working group "fish tests" in the main committee " Detergents " (15.10.73)
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(4) not assignable

16.11.2001 (1)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	other
Species	:	other: Daphnid
Exposure period	:	48 hour(s)
Unit	:	g/l
Analytical monitoring	:	
EC50	:	= 1210
Method	:	other: Calculated (ECOSAR Program) (v0.99e)
Year	:	1999
GLP	:	no
Test substance	:	other TS: molecular structure
Remark	:	The EC50 value is greater than the water solubility (160 g/l).
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(2) valid with restrictions

13.02.2001 (12)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Green
Endpoint	:	other
Exposure period	:	96 hour(s)
Unit	:	g/l
Analytical monitoring	:	
EC50	:	= 584
Method	:	other: Calculated (ECOSAR Program) (v0.99e)
Year	:	1999
GLP	:	no
Test substance	:	other TS: molecular structure
Remark	:	The EC50 value is greater than the water solubility (160 g/l).
Source	:	Bayer Corporation Pittsburgh
Reliability	:	(2) valid with restrictions

12.12.2000 (12)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic

Species	:	activated sludge
Exposure period	:	3 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	> 10000
Method	:	other: Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192
Year	:	1988
GLP	:	no
Test substance	:	
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Test condition	:	direct weight

25.05.1994 (1)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	60
Vehicle	:	water
Value	:	= 3050 mg/kg bw
Method	:	other: Fink and Hund, Arzneim. - Forsch. 15, 1965, p. 624
Year	:	1965
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	There were 10 animals used at each dose level. The doses were: 1.0 g/kg, 2.0 g/kg, 3.1 g/kg, 3.5 g/kg, 3.8 g/kg and 4.0 g/kg.
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(2) valid with restrictions

12.12.2000 (8)

Type	:	LD50
Species	:	rat
Strain	:	no data
Sex	:	
Number of animals	:	
Vehicle	:	CMC
Value	:	ca. 2560 mg/kg bw
Method	:	
Year	:	1979
GLP	:	
Test substance	:	
Result	:	Clinical observations were reduced activity, reduced grip strength, cyanosis, reduced pain reflex, disturbances of co-ordination, and anomalies of position. Dose-response information is not available. Animals dying showed hemorrhage of the stomach and intestinal mucosa. Surviving animals were without adverse necropsy findings at the end of the 14-day observation period.
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Test substance	:	Calcium Formate, CAS Number 544-17-2
Reliability	:	(2) valid with restrictions

16.11.2001 (4)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 2650 mg/kg bw
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(4) not assignable

16.11.2001 (11)

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 1920 mg/kg bw
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(4) not assignable

16.11.2001 (10)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.v.
Exposure time	:	
Value	:	= 154 mg/kg bw
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Reliability	:	(4) not assignable

16.11.2001 (10)

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	Lifelong
Frequency of treatment	:	Daily
Post obs. period	:	
Doses	:	200 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 200 mg/kg
Method	:	other
Year	:	
GLP	:	no
Test substance	:	
Method	:	

The study design encompassed both a five-generation and chronic study in Wistar rats with calcium formate at 0.2% in drinking water. Eight males and 24 females were in the original test group with four controls of each sex. Both microscopic and pathologic investigations were done upon natural death of the animals.

An additional series of experiments using 0.4% calcium formate in the drinking water was also in progress and was in the second year and second generation at the time of this publication, histopathology results were not available for this dose level.

Remark :
Limitations to this study include the lack of data presentation for the 0.4% dose group, the limited description of the pathology and histopathology organ list and the modest size of the concurrent control group.

Result :
Bodyweights and bodyweight gains of treated and control animals were similar. Microscopic and histological investigation of lung, spleen, stomach, liver and kidneys showed no suspect findings. Occasional small phagocytic action in reticuloendothelium and reticulo-histocyto elements of lung, spleen and stomach lymph nodes were reported. Two benign spontaneous tumors were seen in old animals and were considered not related to test substance administration.

The study at 0.4% calcium formate had been going on for about two years and it was reported that no disturbances (presumably mortality, body weight, fertility, or developmental toxicity) had been observed up to this point. Pathology and histopathology were in progress pending natural death of the test animals.

Source : Bayer Corporation Pittsburgh
Test substance : Calcium Formate, CAS Number 544-17-2
Reliability : (2) valid with restrictions
18.11.2001 (10)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium TA 1535, TA 100, TA 1537, TA 98
Concentration : up to 12,500 ug test substance per plate
Cycotoxic conc. : greater than 12,500 ug/plate in all strains
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year : 1983
GLP : yes
Test substance : other TS: purity > 99%
Source : Bayer AG Leverkusen
Bayer Corporation Pittsburgh
Test condition :
The following concentrations of calcium formate were tested:
20, 100, 500, 2500, and 12,500 ug/plate.

Positive controls: Sodium azide (only TA 1535)
Nitrofurantoin (only TA 100)
4-Nitro-1,2-phenylene diamine
(only TA 1537 and TA 98)
2-Aminoanthracene

Solvents used: Deionized water was used with calcium formate and DMSO was used with the positive controls.

S9 mix was used for the stimulation of mammalian metabolism. It was made from the livers of adult male Sprague Dawley rats.

Reliability : (1) valid without restriction
07.11.2001 (2)

5.7 CARCINOGENITY

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	3 years
Frequency of treatment	:	daily
Post. obs. period	:	no
Doses	:	0.2% (3 years), 0.4 % (2 years, pathology not reported)
Result	:	
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	The study design encompassed both a five-generation and chronic study in Wistar rats with calcium formate at 0.2% in drinking water. Eight males and 24 females were in the original test group with four controls of each sex. Both microscopic and pathologic investigations were done upon natural death of the animals. An additional series of experiments using 0.4% calcium formate in the drinking water was also in progress and was in the second year and second generation at the time of this publication, histopathology results were not available for this dose level.
Remark	:	Limitations to this study include the lack achieving a maximum tolerated dose, the modest size of the male F1 group, and the size of the concurrent control group. No of animals: 8 males and 24 females per dose in the F1 group.
Result	:	Bodyweights and bodyweight gains of treated and control animals were similar. Microscopic and histological investigation of lung, spleen, stomach, liver and kidneys showed no suspect findings. Occasional small phagocytic action in reticuloendothelium and reticulo-histocyto elements of lung, spleen and stomach lymph nodes were reported. Two benign spontaneous tumors were seen in old animals and were considered not related to test substance administration. The study at 0.4% calcium formate had been going on for about two years and it was reported that no disturbances (presumably mortality, body weight, fertility, or developmental toxicity) had been observed up to this point. Pathology and histopathology were in progress pending natural death of the test animals.
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Test substance	:	Calcium Formate, CAS Number 544-17-2
Conclusion	:	Signs of a chronic intoxication could not be detected by macroscopic or histopathological examinations. There was no increased tumor-rate.
Reliability	:	(2) valid with restrictions

18.11.2001 (10)

5.8 TOXICITY TO REPRODUCTION

Type	:	Fertility
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	2-5 generations
Frequency of treatment	:	daily
Premating exposure period		
Male	:	6 weeks
Female	:	6 weeks
Duration of test	:	lifelong
Doses	:	0.2 % (5 generations); or 0.4 % (2 generations)
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	200 mg/kg bw
NOAEL F1 Offspr.	:	200 ml/kg bw
Method	:	other
Year	:	
GLP	:	no
Test substance	:	no data
Method	:	The study design encompassed both a five-generation and chronic study in Wistar rats with calcium formate at 0.2% in drinking water. Eight males and 24 females were in the first generation group with four controls of each sex. The fertility of treated animals after 6, 7 or 10 weeks of administration was compared with the fertility of control after 8 weeks of study start. The text of this report indicates that a study with 0.4% calcium formate using the same protocol is in progress and in the second generation with no "disturbances" observed. Thus, it appears that 0.4% calcium formate does not have an adverse effect on fertility. As data were not provided, however, the 0.2% level is considered the reproductive NOEL in this study.
Remark	:	Limitations to this study include the lack of data presentation for the 0.4% dose group; not achieving maternal toxicity at the high dose level; and lack of details concerning reproductive parameters evaluated beyond number, weight and length of pups. No. of animals: 8 males and 24 females per dose level.
Result	:	Numbers of offspring, body weights and body lengths were not different for treated animals as compared with controls. No maternal toxicity was observed, no adverse effects on the offspring were observed on examination.
Source	:	Bayer AG Leverkusen Bayer Corporation Pittsburgh
Test substance	:	Calcium Formate, CAS Number 544-17-2
Conclusion	:	No reduction of fertility; no maternal toxicity; no embryotoxic or teratogenic effects were observed under these conditions. The NOEL for reproduction is 0.2% in drinking water or ca. 200 mg/kg.
Reliability	:	(2) valid with restrictions

18.11.2001 (10)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	Continuous during entire period of gestation and at least six weeks prior to gestation.
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	200 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	200 mg/kg bw
NOAEL Teratogen	:	200 mg/kg bw
Method	:	other
Year	:	
GLP	:	no
Test substance	:	
Method	:	The study design encompassed both a five-generation and chronic study in Wistar rats with calcium formate at 0.2% in drinking water. Eight males and 24 females were in the first generation group with four controls of each sex. The fertility of treated animals after 6, 7 or 10 weeks of administration was compared with the fertility of control after 8 weeks of study start. A portion of the pups were sacrificed shortly after birth for evaluation of developmental toxicity. The text of this report indicates that a study with 0.4% calcium formate using the same protocol is in progress and in the second generation with no "disturbances" observed. Thus, it appears that 0.4% calcium formate does not have an adverse effect on developmental toxicity. As data were not provided, however, the 0.2% level is considered the developmental NOEL in this study.
Remark	:	Limitations to this study include the lack of data presentation for the 0.4% dose group, not achieving maternal toxicity at the high dose level, and lack of details concerning evaluation of the pups for major malformations and variations.
Result	:	No statisical difference in organ and bone abnormalitites. Growth of treated offspring was similar to controls.
Source	:	Bayer Corporation Pittsburgh
Test substance	:	Calcium Formate, CAS Number 544-17-2
Conclusion	:	No reduction of fertility, maternal toxicity, embryotoxic or teratogenic effects were observed under these conditions. The NOEL for developmental and maternal toxicity is 0.2% in drinking water or ca. 200 mg/kg.
Reliability	:	(2) valid with restrictions

18.11.2001 (10)

(1) Bayer AG data

(2) Bayer AG data, Report No. 17969, 25. 4. 1989

(3) Bruns: Bayer AG, Leverkusen, 22. 2. 1988

(4) Degussa AG data, Akute Toxizitaetspruefung von 'Calciumformiat'nach oraler Applikation an der Ratte, Degussa-US-IT-Nr. 79-0029-DKT, 1979/january

(5) Degussa AG data, Pruefung von Calciumformiat in Augenreiz-test am Kaninchen, Degussa-US-IT-Nr. 78-0016-DKT, 1978/november

(6) Degussa AG data, Pruefung von Calciumformiat in Hautreiz-test am Kaninchen, Degussa-US-IT-Nr. 78-0015-DKT, 1978/november

(7) EPIWIN 3.05, Syracuse Research Corp, Syracuse NY 13210

(8) Loeser, E.: Bayer AG data, short report, 21. 4. 1978

(9) Lyman et al. Handbook of Chemical Property Estimation Methods, American Chemical Society, Washington DC 1990.

(10) Malorny, J. V.: Zeitschrift fuer Ernaehrungswissenschaft 9, 332-339 (1969)

(11) Marhold, J. V.: Sbornik Vysledku Toxixologickeho Vysetreni Latek A Pripravku, Institut Pro Vychovu Vedoucicn Pracovniku Chemickeho Prumyclu, Praha, Czechoslovakia, 66 (1972)

(12) Meylan W. and Howard P. (1999) EPIWin Modeling Program. Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

(13) The Condensed Chemical Dictionary 9th Edition (1977) Hawley, G.G, Van Nostrand Reinhold Co., New York. p.151

(14) The Merck Index 10th Edition (1983) Rahway, New Jersey. p. 230

(15) Thyssen, J.: Bayer AG data, short report, 20. 9. 1978

I U C L I D

Data Set

Existing Chemical	:	ID: 107-31-3
CAS No.	:	107-31-3
EINECS Name	:	methyl formate
EINECS No.	:	203-481-7
TSCA Name	:	Formic acid, methyl ester
Molecular Formula	:	C2H4O2
Memo	:	
Printing date	:	20.12.2001
Revision date	:	
Date of last Update	:	20.12.2001

1.0.1 OECD AND COMPANY INFORMATION

Type	:	lead organisation
Name	:	American Chemistry Council, Formates Panel
Partner	:	
Date	:	
Street	:	1300 Wilson Boulevard
Town	:	22209 Arlington, VA
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	

25.05.2001

Type	:	cooperating company
Name	:	Celanese Ltd
Partner	:	
Date	:	
Street	:	
Town	:	
Country	:	
Phone	:	
Telefax	:	

Telex :
Cedex :
20.12.2001

Type : cooperating company
Name : Bayer Corporation
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
20.12.2001

Type : cooperating company
Name : BASF Corporation
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
20.12.2001

Type : cooperating company
Name : GEO Specialty Chemicals
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
20.12.2001

Type : cooperating company
Name : Hercules Inc
Partner :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
20.12.2001

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Purity : % w/w
13.12.2000

1.2 SYNONYMS

Ameisensaeuremethylester
30.01.2001

Formic Acid Methyl ester
30.01.2001

Formic acid, methyl ester (6CI, 8CI, 9CI)
30.01.2001

Methanoic acid methyl ester
30.01.2001

Methyl formate
30.01.2001

Methyl methanoate
30.01.2001

Methylformiat
30.01.2001

R 611
30.01.2001

2.1 MELTING POINT

Value : ca. -100 ° C
Remark : Handbook value
Reliability : (2) valid with restrictions
19.11.2001 (25)

Value : = -100.4 ° C
Reliability : (2) valid with restrictions
18.11.2001 (10)

2.2 BOILING POINT

Value : = 31.5 ° C at 760
Remark : Handbook value
Reliability : (2) valid with restrictions
18.11.2001 (25)

Value : = 32.3 ° C at 760
Reliability : (2) valid with restrictions
18.11.2001 (11)

2.3 DENSITY

Type : relative density
Value : = .987 at 15° C
Remark : Handbook value
Reliability : (2) valid with restrictions
18.11.2001 (25)

Type : density
Value : = .968 g/cm3 at 20° C
Reliability : (2) valid with restrictions
18.11.2001 (10)

2.4 VAPOUR PRESSURE

Value : = 644 hPa at 20° C
Reliability : (2) valid with restrictions
18.11.2001 (10)

Value : = 780 at 25° C
Remark : Given as 585.7 mm Hg, converted to hPa
Reliability : (2) valid with restrictions
19.11.2001 (15)

2.5 PARTITION COEFFICIENT

Log pow : = -.21 at 25° C
Method OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1988
GLP : no data

Test substance :
Reliability : (2) valid with restrictions
19.11.2001 (5) (10)

Log pow : = .03 at ° C
Remark : Literature value
Reliability : (2) valid with restrictions
19.11.2001 (19)

Log pow : = -.17 at ° C
Method other (calculated)
Year :
GLP :
Test substance :
23.05.2001 (16)

2.6.1 WATER SOLUBILITY

Value : = 300 g/l at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : = 4 - 5 at 200 g/l and 20 ° C
Reliability : (2) valid with restrictions
18.11.2001 (10)

Value : = 30 vol% at ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Remark : Handbook value
Reliability : (2) valid with restrictions
18.11.2001 (25)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1500000 molecule/cm3
Rate constant	:	= cm3/(molecule*sec)
Degradation	:	% after
Remark	:	ca. 50 % after 71 day Based on 12-hour day
Result	:	Rate Constant: 0.227 (+/-0.034)*10-12 cm^3/molecule*sec at 296 K
Reliability	:	(2) valid with restrictions Calculated by an acceptable method.

20.12.2001 (17)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	= 5.1 day at 25 degree C
t1/2 pH9	:	at degree C
t1/2 pH 8	:	= 12.3 hour(s) at 25 degree C
Deg. Product	:	
Method	:	other (calculated)
Year	:	2001
GLP	:	no
Test substance	:	no data
Remark	:	These vlaues are directly from from the HYDROWIN 1.67 program and are based on the Kb calculated by HYDROWIN
Reliability	:	(2) valid with restrictions

19.11.2001 (13)

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	= 52 hour(s) at 25 degree C
t1/2 pH9	:	= .5 hour(s) at 25 degree C
Method	:	Calculated from experimental Kb
Remark	:	These are calculated t1/2 values using a value for Kb found in the literature. The pH 4 t1/2 was not calculated because there is also a mechanism for acid based hydrolysis and the vale derived for the base hydrolysis rate constant may give an unreliable estimate.
Result	:	Experimental Kb = 3.66 L/mol-sec
Reliability	:	(2) valid with restrictions Calculated from experimental data by an acceptable method.

19.11.2001 (18)

3.1.3 STABILITY IN SOIL

Type	:	other
Radiolabel	:	

Concentration :
Soil temp. : degree C
Soil humidity :
Soil classif. :
Year :
Remark : Based upon an estimated Koc of 5, methyl formate is ex–pected to leach readily in soil.
Source: BASF AG Ludwigshafen
Reliability : (2) valid with restrictions
Calculated with an acceptable method.

18.11.2001 (20)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level III
Year : 2001
Method : EPIWIN level III model with measured VP, Herry's Law constant and Kow
Remark : Values for half-lives of air, water and soil were adjusted from the defaults based on available data. The experimental Ko/w and vapor pressure was also used in the calculation.
Result : Chem Name : Methyl Formate
Molecular Wt: 60.05
Henry's LC : 0.000223 atm-m3/mole (Henry database)
Vapor Press : 586 mm Hg (user-entered)
Log Kow : -0.21 (user-entered)
Soil Koc : 0.253 (calc by model)

	Concentration (%)	Half-Life (hr)	Emissions (kg/hr)
Air	35.9	1180	1000
Water	36.9	120	1000
Soil	27.1	120	1000
Sediment	0.0618	1440	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	5.57e-010	80.7	1.37e+003	2.69	45.6
Water	2.61e-009	812	141	27.1	4.68
Soil	6.93e-008	598	0	19.9	0
Sed	2.17e-009	0.113	0.00471	0.00378	0.000157

Persistence Time: 127 hr
Reaction Time: 256 hr
Advection Time: 252 hr
Percent Reacted: 49.7
Percent Advected: 50.3

Half-Lives (hr), (based upon user-entry):
Air: 1176
Water: 120
Soil: 120
Sediment: 1440

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Reliability : (2) valid with restrictions
19.11.2001 (14)

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, non-adapted
Concentration	:	51.7mg/l related to Test substance 20mg/l related to DOC (Dissolved Organic Carbon)
Contact time	:	28 day
Degradation	:	= 90 - 100 % after 28 day
Result	:	readily biodegradable
Kinetic of test substance	:	7 day = 77 **%** 14 day = 91 **%** 21 day = 93 **%** 28 day = 93 **%** **%**
Control substance	:	Aniline
Kinetic	:	14 day = 72 **%** 28 day = 91 **%**
Deg. Product	:	
Method	:	
Year	:	1997
GLP	:	yes
Test substance	:	
Method	:	The protocol was the same as the current ISO 14593 [Water quality -- Evaluation of ultimate aerobic biodegradability of organic compounds in aqueous medium -- Method by analysis of inorganic carbon in sealed vessels (CO2 headspace test)] but was conducted prior to the ISO protocol being accepted as an international standard. The procedure was also in accord with the current EPA guideline OPPTS 835.3120 (Sealed-Vessel CO2 Production Test).
Result	:	Although the data fulfilled all OECD criteria for ready biodegradation of the material, the initial report only classified the material, "biologically degradable". This was because at the time the report was written the official method was still in the design phase. Since it is now an international standard, the classification can now be evaluated as "Readily Biodegradable" based on the data presented for both the CO2 evolution and the removal of DOC.
Test substance	:	Methyl formate, purity 97.3%
Conclusion	:	The test material is readily biodegradable
Reliability	:	(1) valid without restriction

09.07.2001 (6)

Type	:	aerobic
Inoculum	:	activated sludge
Contact time	:	
Degradation	:	> 90 % after 7 day
Result	:	
Conclusion	:	The material is biodegradable
Reliability	:	(4) not assignable

18.11.2001 (8)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	m = 46
LC0	:	m = 46
LC50	:	m ca. 120
LC100	:	m <= 215
Method	:	other
Year	:	1989
GLP	:	
Test substance	:	
Method	:	Based on a range-finding study, concentrations were fixed at 10.0, 21.5, 46.4, 100 and 215 mg/L. Test material was directly added to reconstituted fresh water (total hardness 2.5 mmol/L, acid capacity 0.8 mmol/L, pH about 8). Fish, body length 6.3 to 7.5 cm, were added to 10 liter containers of water in groups of 10 at each concentration plus control using all-glass aquaria at 21° C. Mortality was determined at 1, 4, 24, 48, 72, and 96 hours.
Remark	:	The volatility of methyl formate is a concern in this static study using nominal concentrations of methyl formate. As no analytical measurements were conducted, the final concentration of methyl formate may have been much lower due to volatilization and base-catalyzed hydrolysis. The 24-hour result is considered reliable. The lack of additional mortality after 48 hours is consistent with volatilization or hydrolysis. The predicted Henry's Law constant indicates that volatilization will be relative slow in comparison to the duration of the test. Hydrolysis, however, might be a significant means of test material loss. The half live for hydrolysis calculated from the hydroxyl ion concentration at pH 7.4 (the nominal pH during the test) and the Kb of 15.7 L/mol-sec (derived from Hydrowin) is 48 hours. Therefore, significant loss of test material to hydrolysis is expected during the 96 hours of the test. The concentration of non-hydrolyzed test material at the end of the test would be about 25% of the original. The result is supported by the ECOSAR prediction using the ester model of a 96-hour LC50 of 132 mg/L. This is of the same magnitude as the highest concentration of Methyl formate (500 mg/L) reduced by hydrolysis and evaporation to the range of 100 mg/L by the end of the 96-hour study
Result	:	Mortality was as follows:

Nominal

Conc	# fish	2h	4h	24	48	72	96
10.0	10	0	0	0	0	0	0
21.5	10	0	0	0	0	0	0
46.4	10	0	0	0	0	0	0
100.0	10	0	0	1	3	3	3
215.0	10	0	0	10	10	10	10

Adverse clinical sighs were limited to "tumbling" for the 100 mg/L group at the 24 hour observation and the 215 mg/L group at the 4 hour observation

Oxygen levels and pH remained within normal ranges throughout the study. The recorded temperature remained at 21° C at all measurements.

The ca 115 mg/L LC50 was interpolated from these data.

Source : BASF AG Ludwigshafen
Test substance : Methyl formate, purity 97.7%
Conclusion : The 24-hour LC50 for methyl formate in this study is > 100 mg/L.
Reliability : (2) valid with restrictions
18.11.2001

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no
EC0 : m = 500
EC50 : m > 500
EC100 : m > 500
Method : Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year : 1988
GLP : no
Test substance :
Method :

The study was run in accord with the EU guideline 79/831 EWG Annex C2, without any concentration analysis. Five daphnids were exposed per container with four container per concentration for a total of 20 daphnids per concentration. Concentrations were 0, 62.5, 125, 250 and 500 mg/L. A 500 mg/L stock was prepared and diluted to produce the dilution series. THe test was conducted in filtered tap water with a hardness of 2.7 mmol/L at a pH of 7.7 to 8.3.

Remark :

The test material was susceptible to volatility and base-catalyzed hydrolysis and as no analytical measurements were taken, the actual concentrations during the test are not known.

Concerning the possible volatility of methyl formate in this study conducted under static conditions, although methyl formate has a high vapor pressure, it is hydrophilic and hence binds to water reducing its rate of volatilization from aqueous media. The Henry's Law constant for methyl formate of 2.23E-4 atm-m3/mole (found in EPIWIN 3.05 Henry's Law experimental dataset) is in a range where atmospheric loss during a study will occur but probably would not be highly significant under normal experimental conditions.

Base catalyzed hydrolysis, however, is expected to be a significant source of test material conversion to hydrolysis products. Using the measured Kb at 25° C, and a typical pH reported during this study of 8.0, the initial concentration

of 500 mg/L would be expected to fall to about 30 mg/L after 24 hours (four half-lives) and to about 2 mg/L by the end of the 48 hour study. As the temperature was a bit lower than 25°C, the levels may not have fallen as much due to hydrolysis but it is expected that the vast majority of the initial methyl formate would be converted to methanol and formic acid by the end of the 48-hour test period.

Although the concentration of test material and hydrolysis products cannot be established with certainty, the results are considered sufficient for characterization of the toxicity of Methyl formate to invertebrates because under environmental conditions rapid hydrolysis will also occur and the initial level was five times the maximum level recommended for a limit test under current OECD guidance.

Result : There was no mortality at any time or concentration thoughout the test.
Test substance : Methyl formate, purity 97%
Conclusion : The 48-hour EC50 for this material is greater than 500 mg/L based on nominal concentrations
Reliability : (2) valid with restrictions
10.07.2001 (7)

Type :
Species : other aquatic crustacea: Chaetogammarus marinus
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring :
NOEC : m = 32
EC0 : m = 320
Method :

exposure time: 24-96 h;
LC0 and LC100 based on nominal concentration
organism length= 5 mm
glass stoppered conical flasks were used
initial pH of medium =8
medium = sea water
temperature: 15 deg C
salinity: 28 o/oo
renewal every 24 hours
Test in duplicate, 10 animals per vessel
volume = 1000 sea water
no analysis
Concentrations = 1, 10, 32, 100, 320, 560, 1000 mg/L
pH varied from 7.9 at 0 mg/L to 6.9 at 1000 mg/L

Test substance : Methyl formate, Fluka AG, Purity > 97%
Reliability : (2) valid with restrictions
18.11.2001 (1)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	
EC50	:	c = 190
EC20	:	c = 90
Method	:	other: Scenedesmus-Zellvermehrungs Hemmtest, DIN 38412 Teil 9,
Year	:	
GLP	:	
Test substance	:	
Remark	:	EC90(72h) >500 mg/l.
Source	:	BASF AG Ludwigshafen
Reliability	:	(2) valid with restrictions

24.05.2001 (9)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	
Vehicle	:	
Value	:	ca. 1500 mg/kg bw
Method	:	
Year	:	1979
GLP	:	no
Test substance	:	
Method	:	The test material in aqua dest. was administered at a volume of 10 mg/kg to group of 5 Sprague-Dawley rats of each sex. Five dose levels were administered and animals were observed for 14 days prior to sacrifice and necropsy. The age of rats was not reported; however, bodyweights are provided.
Result	:	The following mortality was recorded, all deaths occurred within the first hour after dosing.

DOSE (mg/kg)	Males	Females
2150	5/5	5/5
1470	2/5	2/5
1000	0/5	0/5
681	0/5	0/5
464	0/5	0/5

The following clinical signs were reported

Dose	Signs
2150	Irregular respiration Apathy Staggering Spastic gait Cyanotic Poor general appearance Shortness of breath
1470	Irregular respiration Apathy Staggering Poor general appearance
1000	Irregular respiration Apathy Poor general appearance
681	none reported
464	none reported

The flowing necropsy observation were reported in animals dying from exposure:

Lungs: Bloodfilled with edema

Stomach: Erosion of the glandular stomach
Heart: Dilation
Intestine: Irritation

Body weights were as follows:

Males: mean body weights

		DAYS AFTER TREATMENT		
Dose	0-day	2-4	7	14
2150	190	-	-	-
1470	270	300	321	344
1000	270	289	317	336
681	260	288	312	329
464	200	231	252	277

Females: mean body weights

Dose	0-day	2-4	7	14
2150	180	-	-	-
1470	180	192	208	211
1000	190	216	222	232
681	200	223	228	231
464	210	232	240	244

Test substance : methyl formate, purity 98 %
Conclusion : The Acute oral LD50 for rats is about 1500 mg/kg
Reliability : (2) valid with restrictions
23.05.2001 (2)

Type : LD50
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 1600 mg/kg bw
Method :
Year : 1972
GLP :
Test substance :
Remark : The value refers to LD50/24 hours and ND50 (narcotic dose 50%) according to the authors.
24.05.2001 (23)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals :
Vehicle :
Exposure time : 4
Value : > 21 mg/l
Method : other
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Three male and three female animals were treated using

whole-body exposure to vapors of test material for 4 hours. Animals were housed individually. Males were 8-weeks old and weighed between 298 and 314 grams at the time of the exposure. Females were 10 weeks old and weighed between 216 and 229 grams. The target and nominal concentrations were 20 mg/L. Actual concentration was measured once an hour during the exposure using a MIRAN 1A Ambient Air analyzer. Mean measured concentration was 21 mg/L over the 4-hour exposure. Temperature during the exposure ranged from 76 to 78 °F., relative humidity ranged from 48 to 50%. Rats were observed daily for adverse clinical manifestations for seven days after exposure and were sacrificed without post-mortem exposure.
-

Remark : This study is considered key and considered reliable for establishing the LC50 value even though it does not meet the current OECD guideline. The study was conducted under glp conditions and the nominal and measured concentrations of test substance were similar. Animals showed few serious clinical signs during the exposure and recovered rapidly.
-

Result : All animals survived the duration of the study. Observations noted during exposure included lacrimation, reduced activities, and eyes closed. Signs exhibited upon removal from the chamber and during the two-hour poet-exposure period were limited to a few secretory signs and ano-genital staining. Virtually no adverse sings were exhibited by animals during the 7-day observation period. Animal weights were recorded prior to exposure and at the end of the 7-day observation period. All animals gained weight during this period and the body weight date were considered unremarkable by the study director.
-

Conclusion : The 4-hour inhalation LC50 in rats is greater than 21 mg/L
Reliability : (2) valid with restrictions
13.07.2001 (12)

Type : LC50
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 20
Vehicle :
Exposure time : 4 hour(s)
Value : > 5.2 mg/l
Method : other
Year : 1979
GLP : no
Test substance : other TS
Method :

Ten male and ten female rats were exposed by whole body inhalation to vapors of the test substance at a nominal concentration of 19.4 mg/L (measured concentration of 5.2 mg/L). Animals were housed five per wire cage during the exposure. Exposure concentration was determined by gas chromatography. Animals were observed for 14 days after the exposure sacrificed and necropsied.

Remark : This study is considered supporting information.
Result :

No animal died during the study. Clinical signs were limited to watering eyes and ruffled fur and were cleared after day 2 of the study. Some males showed hair loss on the muzzle.

Body weights (mean)

	Males wt (g)		Females wt (g)	
Day	Test	Control	Test	Control
Start	187	188	189	187
Day 7	224	218	203	197
Day14	260	267	213	206

Test condition :
Methylformate. Prod. Nr 04837Purity 98%
Reliability : (2) valid with restrictions
23.05.2001 (3)

Type : other
Species : other
Strain : no data
Sex : no data
Number of animals :
Vehicle :
Exposure time :
Method :
Year : 1941
GLP : no
Test substance :
Method : Results of the exposure of unspecified (presumably rats) experimental animals to the vapors of methyl formate are presented in this brief report of experimental findings. No experimental details were presented.
Remark : This study is considered supporting
Result : The following results are provided:

Kills most animals in a short time	50,000 ppm
Dangerous to life in 30 to 60 minutes	15,000 - 25,000 ppm
Maximum concentration tolerated for 60 min without serious disturbances	5,000 ppm
Maximum concentration for prolonged (8 hours) exposure without serous disturbances	1,500-2000 ppm

The conclusions also stares that narcosis and irritation were identified as effects of acute vapor esposure
Test condition : Methyl formate, purity unspecified
Conclusion : The acute LC50 is greater than 5000 ppm for 1 hour and 2000 ppm for 8 hours.
Reliability : (4) not assignable
23.05.2001

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Value : > 4000 ml/kg bw

Method	:	
Year	:	1978
GLP	:	
Test substance	:	
Method	:	Rats were treated and observed for 14 days, no other information
Remark	:	This result is supported by a 1990 screening-level dermal toxicity study of methyl formate sponsored by Hoechst Celanese in which 0/4 treated rabbits died at a dermal dose of 5,000 mg/kg (BioDynamics Inc, Acute Dermal Toxicity, Rabbits C-1160, sponsored by Hoechst Celanese, 2/28/1990)
Result	:	The LD50 was found to be > 4000 mg/kg. The following clinical signs were observed: Slight apathy Staggering Spastic gait irregular breathing
Test substance	:	Methyl Formate, purity 98%
Reliability	:	(4) not assignable

11.09.2001 (3)

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	no data
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	1.5 years
Frequency of treatment	:	Continuous
Post obs. period	:	none
Doses	:	1% (= 274 mg/animal formate or 185 mg/animal calculated to formic acid according to the authors)
Control group	:	no data specified
Method	:	
Year	:	
GLP	:	no
Test substance	:	
Method	:	Six animals per group
Remark	:	The results are only available as a brief keynote summary.
Result	:	No toxicity detected
Test substance	:	Sodium formate in the drinking water at 1%
Conclusion	:	Sodium formate at 1% in the drinking water did not produce clinically adverse effects in rats after administration for approximately 18 months. The NOEL cannot be determined since pathological investigations had not been conducted.
Reliability	:	(4) not assignable

19.11.2001 (21)

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	Lifelong
Frequency of treatment	:	Daily
Post obs. period	:	
Doses	:	200 mg/kg/day

Control group : yes, concurrent vehicle
NOAEL : = 200 mg/kg
Method :
Year :
GLP : no
Test substance :
Method :

The study design encompassed both a five-generation and chronic study in Wistar rats with calcium formate at 0.2% in drinking water. Eight males and 24 females were in the original test group with four controls of each sex. Both microscopic and pathologic investigations were done upon natural death of the animals.

An additional series of experiments using 0.4% calcium formate in the drinking water was also in progress and was in the second year and second generation at the time of this publication, histopathology results were not available for this dose level.

Remark :

Limitations to this study include the lack of data presentation for the 0.4% dose group, the limited description of the pathology and histopathology organ list and the modest size of the concurrent control group. In addition, this study does not take into account the effect of the methanol produced by hydrolysis of methyl formate.

Result :

Bodyweights and bodyweight gains of treated and control animals were similar. Microscopic and histological investigation of lung, spleen, stomach, liver and kidneys showed no suspect findings. Occasional small phagocytic action in reticuloendothelium and reticulo-histocyto elements of lung, spleen and stomach lymph nodes were reported. Two benign spontaneous tumors were seen in old animals and were considered not related to test substance administration.

The study at 0.4% calcium formate had been going on for about two years and it was reported that no disturbances (presumably mortality, body weight, fertility, or developmental toxicity) had been observed up to this point. Pathology and histopathology were in progress pending natural death of the test animals.

Test substance :

Calcium Formate, CAS Number 544-17-2

Conclusion :

This study shows that the formate portion of methyl formate up to the equivalent of 200 mg/kg as calcium formate has no adverse effect on rats dosed in drinking water.

Reliability : (2) valid with restrictions
19.11.2001

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 1535 TA100 TA1537 TA1538 TA98
Concentration	:	0, 667,1000, 3333, 6667, 10000 micrograms/plate
Cycotoxic conc.	:	No appreciable toxicity up to 10000 micrograms per plate
Metabolic activation	:	with and without
Result	:	
Method	:	
Year	:	1989
GLP	:	yes
Test substance	:	
Method	:	The S-9 was prepared from Aroclor-induced rats. Positive controls were: -With S-9 - 2-Aminoanthracene for all strains -Without S-9 - Sodium azide for TA100 and TA1535 - 2-Nitrofluorene for TA98 and TA1538 - ICR-191 for TA1537 Triple plate test One repeat All strains run with the preincubation method at 667 to 10000 micrograms/plate with a 20 minute preincubation using a sealed tube to prevent loss of test material.
Result	:	There was no increase in the number of revertants for any strain at any concentration level of test substance. No bacterial toxicity was reported at any concentration. The positive and negative controls responded appropriately.
Source	:	Hoechst Celanese
Test substance	:	Methyl formate (C-1160)
Conclusion	:	This material was not mutagenic in the Ames test under these experimental conditions.
Reliability	:	(1) valid without restriction

12.07.2001 (22)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 1535 TA100 TA1537 TA98
Concentration	:	20 to 5000 ug/plate
Cycotoxic conc.	:	no cytotoxicity reported
Metabolic activation	:	with and without
Result	:	
Method	:	OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year	:	1989
GLP	:	no
Test substance	:	
Method	:	The S-9 was prepared from Aroclor-induced rats. Posiitive controls were: -With S-9 - 2-Aminoanthracene for all strains -Without S-9 - MNNG for TA100 and TA1535 - 4-Nitro-o-phenylendiame for TA98 - 9-Aminoacridine chloride for TA1537

Triple plate test

All strains run with the plate-incorporation method and the preincubation method at 20 to 5000 micrograms/plate. Strain 1535 also run with plate incorporation technigue at five concentrations from 100 to 1000 micrograms/plate.

Result : There was no increase in the number of revertants for any strain at any concentration level of test substance. No bacterial toxicity was reported at any concentration. The positive and negative controls responded appropriately.

Source : BASF AG Ludwigshafen

Test substance : Pure methyl formate, purity 98.4%

Conclusion : This material was not mutagenic in the Ames test under these experimental conditions.

Reliability : (2) valid with restrictions

09.07.2001 (4)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Method : Ten workers in a Swiss foundry were monitored at ten different times during work. Neurobehavioral tests were performed to determine if the exposures correlated with changes in neurobehavioral parameters. Tests included postural balance (bipedal, monopedal, bipedal blind) simple reaction time and digit span and a combined memory and reaction-time test. A rating of well being was also recorded as was alcohol, nicotine, caffeine and drug consumption.
.

Remark : In a previous study, these same authors reproved that there was a neurobehavioral effect of isopropanol and methylformate esposure to foundry workers. This was designed as a follow up study and the initial observations could not be repeated.

Result : Mean methyl formate concentration during work was 36 ppm while mean isopropanol concentration was 44 ppm. Three workers exceeded the methylformate MAC value of 100 ppm over 8 hours. The MAC value of 400 ppm for isopropanol was not exceeded. There was no correlation between the results of the neurobehavioral testing and the methylformate concentration.

Personal monitoring and urinary methanol concentrations were found to correlate. No neurobehavioral effects were correlated with exposure.

Conclusion : Combined exposure to methylformate and isopropanol in a foundry did not cause any neurobehavioral effects.

21.09.2001 (24)

Memo : Methylformate and isopropanol exposures in a foundry, neurobehavioural effects

21.09.2001

21.09.2001

(1) Adema,D.M.M., Aquatic toxicity of compounds that may be carried by ships (Marpol 1973, Annex II), A progress report for 1983 and 1984, Delft, TNO, 1984, (Rep.No.R84/59), zitiert nach: ECDIN 07/1993

(2) BASF AG, Abteilung Toxikologie, unveroeffentlichte

(3) BASF AG, Abteilung Toxikologie, unveroeffentlichte Untersuchung (78/495), 22.05.1979

(4) BASF AG, Abteilung Toxikologie, unveroeffentlichte Untersuchung (89/632), 11.01.1990

(5) BASF AG, Analytisches Labor; unveroeffentlichte Untersuchung (J.Nr. 130365/01 vom 12.07.1988)

(6) BASF AG, Labor Oekologie und Umweltanalytic, Prufung der biologischen Abbaubarkeit von Methylformate, rein im CO2-Headspace-Test nach GLP, EN 45001 und ISO 9002, unpublished report 1997

(7) BASF AG, Labor Oekologie; Bestimmung der akute Wirking von Methylformate gegeguber dem Wasserfloh Daphnia magns Straus. Unpublished Report (0074/88) 1988

(8) BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung

(9) BASF AG, Labor Oekologie; unveroeffentlichte Unter–suchung, (0074/88)

(10) BASF AG, Sicherheitsdatenblatt Methylformiat (08.03.1994)

(11) BASF Ag, Sicherheitsdatenblatt Methylformiat (08.03.1994)

(12) BioDynamics Inc, Project 87-8030, An Acute Inhalation Toxicity Study of C-1160 in the Rat. Sponsored by Hoechst-Celanese, 1/06/1988

(13) Calculated using HYDROWIN v 1.67 as found in EPIWIN 3.05

(14) Calculated using the Level III model contained in EPIWIN 3.05 Syracuse Research Corporation 2001.

(15) Daubert TE, Danner, RP. Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, D.C.: Taylor and Francis, 1989 as cited in Hazardous Substance Data Base update of 2/08/2000

(16) EPIWIN 3.04 Calculation

(17) EPIWIN 3.05, Syracuse Research Corp, Syracuse NY 13210

(18) From table in HYDROWIN v1.67 Syracuse Research Corporation 2001

(19) Hansch. C., A. Leo and D. Hoekman. 1995. Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Professional Reference Book. Washington, DC: American Chemical Society.

(20) Lyman,W.J. et al., Handbook of Chemical Property Estima–tion Methods, NY, McGraw–Hill, 4–9, (1982), zitiert nach: HSDB 07/1993

(21) Malorny, G.: Z. Ernaehrungswiss. 9, 332-339 (1969)

(22) Microbiological Associates Inc, Salmonella/Mammalian Preincubation Mutagenicity Assay with a Closed Phase Induction System. Report T8837.502002. 09/27/1989. Sponsored by Hoechst Celanese

(23) Munch J.C.: Industr. Med. Surg. 41 (4), 31 (1972) cited in: Henschler D.: MAK–Begruendung (1974)

(24) Sethre T, Laubli T, Hangartner M, Berode M, Krueger H. Isopropanol and methylformate exposure in a foundry: exposure data and neurobehavioural measurements. Int Arch Occup Environ Health. 2000 Nov;73(8):528-36.

(25) The Merck Index, 10th Edition (1983) Rahway, New Jersey. p. 870

I U C L I D

D a t a S e t

Existing Chemical	Substance ID: 64-18-6
CAS No.	64-18-6
EINECS Name	Formic acid
EINECS No.	200-579-1
Molecular Weight	46.03
Molecular Formula	CH2O2

Producer Related Part

Company:	BASF AG
Creation date:	12-NOV-1992

Substance Related Part

Company:	BASF AG
Creation date:	12-NOV-1992

Memo: Master

Printing date:	09-NOV-2000
Revision date:	01-JUN-1994
Date of last Update:	**24-MAY-2000**

Number of Pages: **80**

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Data Set, Risk Assessment, Directive 67/548/EEC

1.0.1 OECD and Company Information

-

1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: Organic
Physical status: Liquid
Purity: >= 99 % w/w
Remark: The Iuclid Data Sheet is also submitted on behalf of BASF Antwerpen N.V. (B).
The substance-related part is also submitted on behalf of the following companies:

BP Chemicals LTD (GB)
Huels AG,
Kemira OY (SF)
Norsk Hydro A/S (N)
Novo Nordisk A/S (DK)
Perstorp AB (S)
Perstorp SpA, Div. Polyols (I)

15-MAR-2000 (1)

1.1.1 Spectra

-

1.2 Synonyms

Ameisensaeure

Ameisensaure

Aminic acid

Formic acid (7CI, 8CI, 9CI)

Formira

Formisoton

Formylic acid

Hydrogen carboxylic acid

Methanoic acid

Methanoic acid monomer

Myrmicyl

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

-

1.6.1 Labelling

Labelling: As in Directive 67/548/EEC
Symbols: C
Nota: B
Specific limits: Yes
R-Phrases: (35) Causes severe burns
S-Phrases: (1/2) Keep locked up and out of reach of children
(23) Do not breathe vapour
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
Remark: INDEX No. 607-001-00-0
01-MAR-2000 (1) (2) (3)

1.6.2 Classification

Classification: As in Directive 67/548/EEC
Class of danger: Corrosive
R-Phrases: (35) Causes severe burns
Remark: INDEX No. 607-001-00-0
01-MAR-2000 (1) (2) (3)

1.7 Use Pattern

-

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: 5 ml/m3
Short term expos.
Limit value: 10 ml/m3
Schedule: 5 minute(s)
Frequency: 8 times
01-MAR-2000 (1) (4)

Type of limit: MAK (DE)
Limit value: 9 mg/m3
01-MAR-2000 (1) (4)

Type of limit: TLV (US)
Limit value: 9.4 mg/m3
01-MAR-2000 (5) (1)

Type of limit: TLV (US)
Limit value:
Remark: Limit value: 5 ppm
01-MAR-2000 (5) (1)

1.9 Source of Exposure

-

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 1 (weakly water polluting)
01-MAR-2000 (1)

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: No
01-MAR-2000 (1) (6)

1.14.3 Air Pollution

Classified by: TA-Luft (DE)
Labelled by: TA-Luft (DE)
Number: 3.1.7 (organic substances)
Class of danger: III
01-MAR-2000 (1)

1.15 Additional Remarks

-

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: = 8 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

Value: = 8.4 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
24-JAN-2000 (8)

2.2 Boiling Point

Value: = 100.6 degrees C at 1013 hPa
Reliability: (4) Not assignable
Manufacturer / producer data without proof
24-JAN-2000 (8)

Value: = 100.8 degrees C
Reliability: (4) Not assignable
Secondary citation
24-JAN-2000 (9)

Value: = 101 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

2.3 Density

Type: Density
Value: = 1.22 g/cm3 at 20 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

Type: Relative density
Value: = 1.22 at 20 degrees C
Remark: Specific gravity 20/4 °C
Reliability: (4) Not assignable
Handbook
24-MAY-2000 (10)

Type: Density
Value: = 1.2223 g/cm3 at 20 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
24-JAN-2000 (8)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: = 42 hPa at 20 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

Value: = 44 hPa at 20 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
24-JAN-2000 (8)

Value: = 46.7 hPa at 20 degrees C
Reliability: (4) Not assignable
Handbook
24-MAY-2000 (10)

Value: = 72 hPa at 30 degrees C
Reliability: (4) Not assignable
Handbook
24-MAY-2000 (10)

Value: = 170 hPa at 50 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

2.5 Partition Coefficient

log Pow: = -.54 at 20 degrees C
Method: Other (measured)
Year:
Reliability: (2) Valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
24-MAY-2000 (11)

log Pow: = -.492
Method: Other (calculated): Increment method by Rekker with computer program of CompuDrug Ltd.
Year:
Reliability: (2) Valid with restrictions
Calculated value in accordance with generally accepted standard methods
24-MAY-2000 (12)

log Pow:
Method:
Year:
Result: Log P oct = -1.55/-0.22 (calculated)
Reliability: (4) Not assignable
Handbook
24-MAY-2000 (10)

2.6.1 Water Solubility

Value: At 20 degrees C
Qualitative: Miscible
pH: 2.2 at 10 g/l and 20 degrees C
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

Value: At 25 degrees C
Qualitative: Miscible
Reliability: (4) Not assignable
Secondary citation
24-JAN-2000 (9)

2.6.2 Surface Tension

-

2.7 Flash Point

Value: = 48 degrees C
Type: Closed cup
Method: Other: DIN 51 755
Year:
Test substance: Formic acid, purity 99%
Reliability: (1) Valid without restriction
National standard specification
04-MAY-2000 (13)

2.8 Auto Flammability

Value: 480 degrees C
Method: Other: DIN 51 794
Remark: Ignition temperature
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

Value: = 505 degrees C
Method: Other: DIN 51 794
Remark: Ignition temperature
Test substance: Formic acid, purity 99%
Reliability: (1) Valid without restriction
National standard specification
24-JAN-2000 (14)

2.9 Flammability

-

2.10 Explosive Properties

Result: Not explosive
Remark: Because of chemical structure
Reliability: (2) Valid with restrictions
Expert judgement
24-JAN-2000 (15)

2.11 Oxidizing Properties

Result: No oxidizing properties
Remark: Because of chemical structure
Reliability: (2) Valid with restrictions
Expert judgement
24-JAN-2000 (15)

2.12 Additional Remarks

Result: Explosive limits in air: 13.5 - 36.5 vol.%
Test substance: Formic acid, purity 99%
Reliability: (2) Valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
24-JAN-2000 (14)

Result: Viscosity: 1.8 mPa.s at 20 °C

Explosion limits: 12 - 38 vol.%

Hazardous reactions:
Exothermic reaction with: alkalis, amines or products containing amines
Thermal decomposition products: carbon monoxide
Reliability: (4) Not assignable
Manufacturer / producer data without proof
04-MAY-2000 (7)

3.1.1 Photodegradation

Type: Air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Degradation: = 50% after 35.7 days
Method:
Year: **GLP:**
Test substance:
Remark: Rate constant: 4.5*10^-13 cm^3/mol*sec
Test condition: Gas phase reaction with OH radicals; 25 degrees C
(16)

Type: Other: Water / air
Method:
Year: **GLP:**
Test substance:
Remark: Gas and solution phase rate constants: K(gas)= 3.7*10^-3 cm^3/mol*sec; K(solution)= 2.2*10^-13 cm^3/mol*sec
(17)

Type: Water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Degradation: = 50% after .9 year
Method:
Year: **GLP:**
Test substance:
Remark: Rate constant: 2.5*10^9 M^-1 sec^-1
Test condition: pH=7; temperature 15-25 deg C
(18)

Type: Water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Method:
Year: **GLP:**
Test substance:
Remark: Rate constant: 0.28*10^10 l/mol*sec
Test condition: OH formed by pulsed radiolysis; neutral pH
(19)

Type: Water
Method:
Year: **GLP:**
Test substance:
Result: Rate constants for reaction of OH radicals (297 K) in water with HCOO- (340 +/- 39) x 10e7 mol e-1 sec e-1 and for HCOOH (10.1 +/- 1.3) x 10e7 mol e-1 sec -1.
Reliability: (2) Valid with restrictions
23-NOV-1999 (20)

Type: Water
Method:
Year: **GLP:**
Test substance:
Result: k (HCOOH) = (3.3 +/- 1.0) x 10e5 l mol e-1 sec e-1, k (HCOO-) = (5.0 +/- 0.4) x 10e7 l mol e-1 sec e-1 (298 K)
Reliability: (2) Valid with restrictions
24-NOV-1999 (21)

Type: Other
Method:
Year: **GLP:**
Test substance:
Remark: Rate constant (298 K): K= (10.37 +/- 0.04)*10^-12 cm^3/mol* sec.
(22)

3.1.2 Stability in Water

-

3.1.3 Stability in Soil

-

3.2 Monitoring Data (Environment)

Type of measurement: Other
Medium: Other: Food / rain
Remark: Numerous foodstuffs and beverages, such as milk, cheese, wine, fruits, honey and coffee, contain formic acid; natural concentrations are mentioned in a range of from 1-7,700 mg/kg (FDA,PB 266282).
Formic acid is found in the atmosphere and can be detected in rainwater among others:
Rainwater in Ithaca (USA,1977) - 110 ug/l; rainwater in New Hampshire (USA,1977) - 9.2 ug/l; rainwater in the Taunus (1983/84) - 120 ug/l (Hahn, 1986)
Rainwater in Hanover (1987) - 260 ug/l (Winkeler et al., 1988)
Rainwater in Juelich (1986) - 250 ug/l. (Mueller,1986)
(23)

Type of measurement: Other
Medium: Other: Industrial effluent (paper manufacture)
Remark: Evidence of 18 mg/l (gas liquid chromatography mass spectrometry)
(24)

Type of measurement: Other
Medium: Other: Sewage & effluents (oxidation pond water)
Remark: Evidence of 31 mg/l (gas liquid chromatography mass spectrometry)
(24)

Type of measurement: Other
Medium: Other: Surface water (lake)
Remark: Evidence of 3-18 ug/l (liquid chromatography)
(25)

Type of measurement: Other
Medium: Other: Surface water (Ohio river)
Remark: Evidence of 10-24 ug/l (gas liquid chromatography)
(26)

Type of measurement: Other
Medium: Other: Industrial influent/effluent (kraft pulp)
Remark: Evidence of 18/31 mg/l (influent to /effluent from stabilization basin)
(27)

Type of measurement: Other
Medium: Biota
Remark: Formic acid is a natural substance which is formed biogenically as an intermediate and final product in the microbial, plant and animal metabolism. It is an excretion product of natural acid-forming prokaryotic fermenting organisms. These anaerobes are bacteria which belong to the enterobacteriaceae and are also typically native to the human intestines (e.g. E. coli). Formic acid is moreover formed in the glands of ants and stinging nettles and in other animals and plants.
09-NOV-1999 (23)

Type of measurement: Other
Medium: Other
Remark: Formic acid found in (ppbv): 1. Germany: Continental anticyclone 1.04 +/- 1.08, marine influence 0.17 +/- 0.06; 2. Amazon/basin, ABLE-2A, dry season: 1.6 +/- 0.6 (boundary layer); 3. Amazon/basin, ABLE-2B, wet season: 0.37 +/- 0.24 (boundary layer), 0.15 +/- 0.09 (free troposphere); 4. Central Africa/DECAFE, dry season: 3.7 +/- 1.0 (boundary layer), 0.9 +/- 0.3 (free troposphere).
(28)

3.3.1 Transport between Environmental Compartments

Type: Volatility
Media: Water - air
Method: Other
Year:
Remark: Henry's constant: 1.67*10^-7 atm*m^3/mol (calculated from original citation: "6*10^3 mol l^-1 atm^-1")
The Henry's Law Constant indicates that volatilization from water would not be significant.
(29) (30)

3.3.2 Distribution

Media: Air - biota - sediment(s) - soil - water
Method: Calculation according to Mackay, Level I
Year:
Result: Water: 92%, air: 7.99%, soil: 2.09E-3; sediment: 1.96E-3
Reliability: (1) Valid without restriction
15-NOV-1999 (31)

3.4 Mode of Degradation in Actual Use

-

3.5 Biodegradation

Type: Aerobic
Inoculum: Other: Effluent of a communal sewage treatment plant
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 98% after 14 days
Result: Readily biodegradable
Kinetic:
7 days = 12%
10 days = 26%
13 days = 93%
14 days = 98%
Method: OECD Guideline 301 E "Ready biodegradability: Modified OECD Screening Test"
Year: **GLP:** Yes
Test substance:
Remark: Lag phase: 7 d; degradation phase: 6 d; test duration: 14 d
test substance 72 mg/l initial concentration
Test condition: Neutralized with NaOH
Reliability: (2) Valid with restrictions
15-NOV-1999 (32)

Type: Aerobic
Inoculum: Other: Effluent of a communal sewage treatment plant
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 100% after 11 days
Result: Readily biodegradable
Kinetic:
2 days = 2%
3 days = 4%
7 days = 13%
8 days = 38%
9 days = 100%
Method: OECD Guideline 301 E "Ready biodegradability: Modified OECD Screening Test"
Year: **GLP:** Yes
Test substance:
Remark: Lag phase: 6 d; degradation phase: 3 d; test period: 11 d
Test substance 77 mg/l initial concentration
Test condition: Neutralized with NaOH
Reliability: (2) Valid with restrictions
15-NOV-1999 (33)

Type: Aerobic
Inoculum: Other bacteria: freshwater, acclimatized
Degradation: = 51% after 5 days
Method: Other: Sealed bottle test; (BSB of the THSB)
Year: **GLP:**
Test substance:
Remark: Initial concentration 3-10 mg/l test substance
Test results with a variable test period:
Degree of elimination (10/15/20 d) = 47/39/60%
Test condition: neutralized
(34)

Type: Aerobic
Inoculum: Other bacteria: freshwater, not acclimatized
Degradation: = 48% after 5 days
Method: Other: sealed bottle test; (BSB of the THSB)
Year: **GLP:**
Test substance:
Remark: Initial concentration 3-10 mg/l test substance
Test results with a variable test period:
Degree of elimination (10/15/20 d) = 54/66/68%
Test condition: Neutralized
(34)

Type: Aerobic
Inoculum: Other bacteria: salt water, synthetic
Degradation: = 62% after 5 days
Method: Other: Sealed bottle test; (BSB of the THSB)
Year: **GLP:**
Test substance:
Remark: Initial concentration 3-10 mg/l test substance
Test results with a variable test period:
Degree of elimination (10/15/20 d) = 91/92/95%
Test condition: Neutralized

(34)

Type: Aerobic
Inoculum: Other bacteria: Sewage, communal
Degradation: About 80% after 5 days
Method: Other: Respirometric dilution method; (BSB of the THSB)
Year: **GLP:**
Test substance:
Remark: Dilution series: Initial concentration of the test substance variable from 24-1200 mg/l
13-AUG-1996

(35)

Type: Aerobic
Inoculum: Other bacteria: Freshwater
Concentration: 20 mg/l related to test substance
Degradation: = 40.5% after 5 days
Method: Other: Dilution method; (BSB of the THSB)
Year: **GLP:**
Test substance:

(36)

Type: Aerobic
Inoculum: Other bacteria: Salt water, synthetic
Concentration: 40 mg/l related to test substance
Degradation: = 51.7% after 5 days
Method: Other: Dilution method; (BSB of the THSB)
Year: **GLP:**
Test substance:

(36)

Type: Aerobic
Inoculum: Activated sludge
Concentration: 500 mg/l related to test substance
Degradation: = 70% after 1 day
Method: Other: Warburg method; (BSB of the THSB)
Year: **GLP:**
Test substance:
Remark: Test results with a variable test period:
Degree of elimination (6/12 h) = 28.3/45.4%

(37)

3.6 BOD5, COD or BOD5/COD Ratio

-

3.7 Bioaccumulation

Species:
Exposure period:
Concentration:
BCF: Approx. .22
Elimination:
Method: Other
Year: **GLP:**
Test substance:
Remark: BCF calculated on the basis of the log Pow = -0.54 and the equation "log BCF = 0.76 log Pow -0.23"

(38)

Species:
Exposure period:
Concentration:
BCF:
Elimination:
Method: Other
Year: **GLP:**
Test substance:
Remark: The log Pow measured of -0.54 suggests the absence of a bioaccumulation potential.

(23)

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: Other: No data
Species: Lepomis gibbosus (fish, freshwater)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** No data
LC50: = 5000
Method: Other: Freeman, L.: Sewage Ind. Wastes 25 (7), 845
Year: 1953 **GLP:** No data
Test substance: No data
Remark: Bluegill sunfish
Test substance: Sodium formate
06-SEP-1995 (39) (40)

Type: Other: No data
Species: Lepomis macrochirus (fish, freshwater)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** No data
LC50: = 175
Method: Other: Freeman, L.: Sewage Ind. Wastes 25 (7), 845
Year: 1953 **GLP:** No
Test substance: No data
Remark: The result is only available as a brief secondary citation.
06-SEP-1995 (39) (41)

Type: Static
Species: Leuciscus idus (fish, freshwater)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** No
NOEC: = 100
LC50: = 122
Method: Other: Determination of the effect of water constituents on fish, DIN 38412 part 15
Year: **GLP:** Yes
Test substance: No data
23-OCT-1995 (42)

Type: Static
Species: Leuciscus idus (fish, freshwater)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** No
NOEC: 22
LC50: 46 - 100
Method: Other: Determination of the effect of water constituents on fish, DIN 38412 part 15
Year: 1982 **GLP:** No
Test substance: As prescribed by 1.1 - 1.4
Remark: To assess the physiologic effect of the relatively low pH on the golden orfe the highest test concentration (100 mg/l) was investigated in parallel after adjusting the pH with NaOH approximately to the pH of the control. After the pH adjustment, 100 mg/l was tolerated without mortality and without any symptoms.
23-OCT-1995 (43)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 25
EC50: = 34.2
EC100: = 50
Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: **GLP:**
Test substance:
23-SEP-1999 (44)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 25
EC50: = 34.2
EC100: = 50
Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: **GLP:**
Test substance:
23-SEP-1999 (44)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 151.2
Method: Other: Test for inhibition of swimming ability (immobilization)
Year: **GLP:**
Test substance:
Remark: Confidence limits: 138-165 mg/l
Test condition: 22 degrees C; pH 7.0-8.2

(45)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 120
Method:
Year: **GLP:**
Test substance:
Remark: Immobilization

(46)

Species: Other aquatic arthropod: Artemia salina (naupliar larvae)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : = 410
Method:
Year: **GLP:**
Test substance:

(34)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus quadricauda (algae)
Endpoint:
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
TGK : = 100
Method: Other: Cell multiplication inhibition test
Year: **GLP:**
Test substance:

(46)

Species: Scenedesmus subspicatus (algae)
Endpoint:
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 26.9
EC20 : = 14.9
Method: Other: Scenedesmus cell multiplication inhibition test, DIN 38412 part 9, determination of the inhibitory effect of water constituents on green algae
Year: **GLP:**
Test substance:
Remark: EC90(72h)=45.6 mg/l

(44)

Species: Scenedesmus subspicatus (algae)
Endpoint:
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 25
EC20 : = 12.6
Method: Other: Scenedesmus cell multiplication inhibition test, DIN 38412 part 9, determination of the inhibitory effect of water constituents on green algae
Year: **GLP:**
Test substance:
Remark: EC90(96h)=45.1 mg/l

(44)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: Aquatic
Species: Other bacteria: Activated sludge, adapted
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:**
EC20 : > 1000
Method: Other: Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192
Year: **GLP:**
Test substance:
Remark: If the test substance is properly introduced into adapted biological sewage treatment plants, no disorders of the degradation activity of the activated sludge are expected. No respiratory inhibition of activated sludge up to 1000 mg/l
22-NOV-1999 (47)

Type:
Species: Escherichia coli (bacteria)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
NOEC : = 1000
Method:
Year: **GLP:**
Test substance:
Remark: Below 1000 mg/l without any inhibitory effect on the acid formation by Escherichia coli.

(46)

Type:
Species: Pseudomonas putida (bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:**
EC10: = 33.9
EC50: = 46.7
EC90 : = 59.5
Method: Other: Pseudomonas cell multiplication inhibitory test, DIN 38412 part 8, adopted for yellow publication, determination of the inhibitory effect of water constituents on bacteria
Year: **GLP:**
Test substance:

(44)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

-

4.5.2 Chronic Toxicity to Aquatic Invertebrates

-

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

-

4.6.2 Toxicity to Terrestrial Plants

-

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

Species: Other avian: Red-winged blackbird
Endpoint: Other: Mortality and repellency
Expos. period:
Unit:
LD50 : >= 111
Method: Other
Year: **GLP:** No data
Test substance: No data
Remark: The acute oral toxicity and a "repellency toxicity index" were determined.
07-DEC-1995 (48)

Species: Other avian: Red-winged blackbird
Endpoint:
Expos. period:
Unit: mg/kg bw
LD50 : > 111
Method: Other: Acute toxicity test
Year: **GLP:**
Test substance:
(23)

4.7 Biological Effects Monitoring

-

4.8 Biotransformation and Kinetics

-

4.9 Additional Remarks

Memo: Aedes aegyptii (insect larva): LC50 = 400 mg/l (4 h), or LC50 = 0.04 % v/v (4 h); 22 - 24 °C
13-JAN-2000 (49)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Value: = 1830 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: The result is only available as a table in the form of a secondary citation.
06-SEP-1995 (50) (51)

Type: LD50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Value: = 1210 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: The result is only available as a secondary citation.
06-SEP-1995 (52) (41)

Type: LD50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Value: = 730 mg/kg bw
Method: OECD Guideline 401 "Acute Oral Toxicity"
Year: 1981 **GLP:** No data
Test substance: No data
Remark: 5 males and 5 females were used per dose group (501, 631, 794 and 1000 mg/kg). The observation period was 14 days.
Result: According to the authors, body weight gain was reduced clearly related to the dose.
Test substance: Formic acid 99%
11-SEP-1995 (53)

Type: LD50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Value: = 1100 mg/kg bw
Method: Other: No data
Year: **GLP:** No data
Test substance: No data
Remark: The result is only available as a secondary citation.
07-DEC-1995 (54)

Type: LD50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Value: = 3050 mg/kg bw
Method: Other
Year: **GLP:** No
Test substance: Other TS
Test substance: Calcium formate
23-OCT-1995 (55)

Type: LD50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Value: = 1100 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: 55 animals were used; no further data. The result is only available as a table.
06-SEP-1995 (50) (56) (51)

Type: LD50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Value: = 11200 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Remark: 45 animals were used; no further data. The result is only available as a table.
Test substance: Sodium formate
05-SEP-1995 (56)

Type: LD50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Value: = 1920 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Remark: 45 animals were used; no further data. The result is only available as a table.
Test substance: Calcium formate
05-SEP-1995 (56)

Type: LD50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Value: = 700 mg/kg bw
Method: Other: No data
Year: **GLP:** No data
Test substance: No data
Remark: The result is only available as a secondary citation.
07-DEC-1995 (54)

Type: LDLo
Species: Rabbit
Sex:
Number of Animals:
Vehicle:
Value: > 4000 mg/kg bw
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Test substance: Formic acid
28-JUL-1997 (57)

Type: Other
Species: Dog
Sex:
Number of Animals:
Vehicle:
Value: = 4000 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Remark: Deaths occurred. In the source, supposed methemoglobin formation is described. The original (Fleig 1907) is not available, and von Oettingen (1959) does not mention this effect. The finding seems to be unlikely.
Test substance: Test substance: Sodium formate
05-SEP-1995 (50) (58) (41) (59)

Type: LDLo
Species: Sheep
Sex:
Number of Animals:
Vehicle:
Value:
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Remark: Formic acid (150 mg/kg) was without any adverse effect except for some indications of anorexia.
Test substance: Formic acid
29-JUL-1997 (60)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: = 7.4 mg/l
Method: Other: BASF test
Year: **GLP:** No
Test substance: As prescribed by 1.1 - 1.4
Remark: Whole-body exposure (vapor). 10 males and 10 females were used per group. The animals were observed for 14 days.
05-SEP-1995 (61)

Type: LC50
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 15 minute(s)
Value: = 15 mg/l
Method: Other: No data
Year: **GLP:** No data
Test substance: No data
Remark: The result is only available as a secondary citation.
06-SEP-1995 (54)

Type: Other: IHT
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 50 minute(s)
Value:
Method: Other: Carried out on the basis of the method described by H.F. Smith et al.: Am. Ind. Hyg. Ass.J. 23, 95-107 (1962)
Year: 1962 **GLP:** no
Test substance: As prescribed by 1.1 - 1.4
Remark: Mortality (2/12) after 3 minutes, 5/6 after 10 min. and 6/6 after 30 and 50 min respectively. Exposure to an atmosphere enriched or saturated at 20 degrees C.
06-SEP-1995 (62)

Type: Other: IHT
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: Other: Carried out on the basis of the method described by H.F. Smith et al: Am. Ind. Hyg. Ass. J. 23, 95-107 (1962)
Year: 1962 **GLP:** No
Test substance: Other TS
Remark: No mortality after 30 min. Exposure to an atmosphere enriched or saturated at 20 degrees C.
Lethality after prolonged exposure
Test substance: Formic acid 50% in water
05-SEP-1995 (63)

Type: Other: IHT
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: Other: BASF test
Year: **GLP:** No
Test substance: Other TS
Remark: No mortality after 3-hour exposure to an atmosphere enriched or saturated at 20 degrees C.
Lethality after prolonged exposure.
Test substance: Formic acid 25% in water
05-SEP-1995 (64)

Type: Other: IHT
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: Other: BASF test
Year: **GLP:** No
Test substance: Other TS
Remark: No mortality after 7-hour exposure to an atmosphere enriched or saturated at 20 degrees C.
Test substance: Formic acid 10% in water
05-SEP-1995 (65)

Type: Other: IHT
Species: Rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 10 minute(s)
Value:
Method: OECD Guideline 403 "Acute Inhalation Toxicity"
Year: 1981 **GLP:** No data
Test substance: No data
Remark: Inhalation hazard test: Lethality in 6 of 6 rats used after 10-min exposure to an atmosphere saturated at 20 degrees C (44,168 ppm)
06-SEP-1995 (66)

Type: Other: IHT
Species: Rat
Sex: Male/female
Number of Animals: 6
Vehicle:
Exposure time: 116 minute(s)
Value:
Method: Other: IHT
Year: 1981 **GLP:** No
Test substance: Other TS
Remark: 12/12 rats died after 10 and 116 min by inhalation of an atmosphere that had been saturated with the volatile part of the compound at 20 degrees centigrade. 8/12 rats died after 3 min by inhalation.
Test substance: Formic acid, purity >98%
16-MAY-2000 (67)

Type: LC50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Exposure time: 15 minute(s)
Value: = 6.2 mg/l
Method: Other: No data
Year: **GLP:** No data
Test substance: No data
Remark: The result is only available as a secondary citation.
07-DEC-1995 (54)

5.1.3 Acute Dermal Toxicity

-

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: = 940 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: The result is only available as a secondary citation.
07-DEC-1995 (50) (51) (68) (52)

Type: LD0
Species: Rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: > 300 mg/kg bw
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Remark: Rabbits tolerated a 300 mg/kg s.c. administration without adverse effect.
Test substance: Formic acid
28-JUL-1997 (69)

Type: LDLo
Species: Rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value:
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Remark: Doses of 0.46-1.25 mg/kg caused central nervous system depression, vasoconstriction and diuresis in rabbits; larger doses (about 4 g/kg) produced convulsions and death.
Test substance: Formic acid
29-JUL-1997 (69)

Type: LD50
Species: Mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: = 145 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: 50 animals were used; no further data. The result is only available as a table.
07-DEC-1995 (50) (56) (51) (52)

Type: Other: MLD
Species: Rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: = 239 mg/kg bw
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: Deaths occurred. The result is only available in a table as a secondary citation.
06-SEP-1995 (50)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: Rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: Corrosive
EC classificat.:
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: The various results are only available as secondary citations.
07-DEC-1995 (70) (51) (71) (72) (52) (73)

Species: Rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method: Other: 610 mg open
Year: **GLP:** No
Test substance: No data
Remark: The result is only available as a secondary citation.
Effect: "mild" according to RTECS
06-SEP-1995 (74)

Species: Other: No data
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: Highly corrosive
EC classificat.:
Method: Other
Year: **GLP:** No data
Test substance: No data
23-OCT-1995 (75)

5.2.2 Eye Irritation

Species: Rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: Irritating
EC classificat.:
Method: Other: Application to the cornea
Year: **GLP:** No data
Test substance: No data
06-SEP-1995 (76)

Species: Rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: Irritating
EC classificat.:
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: Method: 122 mg
Effect: "severe" according to RTECS
The result is only available as a secondary citation.
06-SEP-1995 (74)

Species: Other: No data
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: Irritating
EC classificat.:
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: Conjunctivitis, corneal injuries
Origin of the result not comprehensible
06-SEP-1995 (77)

5.3 Sensitization

Type: No data
Species: Human
Number of Animals:
Vehicle:
Result:
Classification:
Method: Other: No data
Year: **GLP:** No data
Test substance: No data
Remark: According to the present secondary source (HSDB), sensitization to formic acid may occur in rare cases in persons who had previously been exposed to formaldehyde.
06-SEP-1995 (76)

5.4 Repeated Dose Toxicity

Species: Rat **Sex:** Male
Strain: Wistar
Route of admin.: Inhalation
Exposure period: 3-8 days
Frequency of treatment: 6 h daily
Post. obs. period: No data
Doses: 0.037 mg/l (20 ppm)
Control Group: Yes, concurrent vehicle
Method: Other
Year: **GLP:** No data
Test substance: No data
Result: No clinical symptoms. On the 3rd day of exposure, the glutathione concentration was reduced in the liver and kidneys and increased in the brain as compared with the control. The cerebral and acid proteinase activity was increased at the end of the test. The hepatic superoxide dismutase activity was below the control level whereas the activity of the ethoxycoumarin deethylase was increased. The activities of cytochrome P450 and ethoxycoumarin deethylase were reduced in the kidneys. No relation of the changes to the duration of exposure.
06-SEP-1995 (78) (79)

Species: Rat **Sex:** Male/female
Strain: Fischer 344
Route of admin.: Inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 days per week, 6 hours a day
Post. obs. period: None
Doses: 0.015; 0.030; 0.061; 0.122; 0.244 mg/l (8, 16, 32, 64, 128 ppm)
Control Group: Yes, concurrent no treatment
NOAEL: .06 mg/l
LOAEL: .12 mg/l
Method: Other
Year: **GLP:** Yes
Test substance: No data
Remark: 10 males and 10 females were used per group. Another 10 males and 10 females per group were used for the clinicopathologic examination which was carried out on the 3rd and 23rd day of the study. The body weights were determined at the beginning and at the end of the study and at weekly intervals in between. The organ weights (thymus, heart, right kidney, lungs, liver and right testis) were determined. Hematologic and biochemical serum examinations as well as gross-pathologic and histopathologic organ examinations were carried out at the end of the study.

Result: All animals used survived. The body weight of the males of the 32 ppm group was slightly but significantly increased at the end of the study. The body weight gains of the males of the 16, 32 and 64 ppm groups were also significantly increased. No definitely substance-related clinical signs of toxicity were observed during the study. The hematologic changes observed were all slight: At the end of the study, the number of neutrophils was significantly but not dose-dependently reduced in animals of both sexes in all dose groups. Other hematologic changes were rather of an incidental nature and not relevant. Furthermore, few and slight changes of the biochemical serum parameters were observed.
No unusual gross lesions were observed. The absolute liver weights were significantly increased in the males of all exposure groups, and the relative liver weights were significantly increased in the three highest dose groups only. The absolute and relative lung weights were significantly reduced in the females of all exposure groups. In the males, the relative lung weights were significantly reduced in all exposure groups, and the absolute lung weights were significantly reduced in the two highest dose groups only. Most of the histopathologic changes at the respiratory and olfactory nasal epithelia were restricted to the highest dose group. The respiratory epithelium mainly showed slight squamous epithelial metaplasias, and the olfactory epithelium showed minimal to slight degenerative changes. In the 32 and 64 ppm groups, a minimal degeneration of the olfactory epithelium was observed in one male in each case.

As compared with the 2-week study (q.v.), there was no increase in the degree of lesions after prolonged exposure. According to the NTP, a NOAEL of 64 ppm (0.122 mg/l) is obtained from the results of this 13-week study, whereas a NOAEL of 32 ppm (0.06 mg/l) is obtained from the results of the 2-week study.

Test substance: Formic acid, approx. 95% with approx. 5% water

11-SEP-1995 (80) (81)

Species: Rat **Sex:** Male/female
Strain: Fischer 344
Route of admin.: Inhalation
Exposure period: 12 days
Frequency of treatment: 5 days per week, 6 hours per day
Post. obs. period: 1 day
Doses: 0.06; 0.12; 0.24; 0.48; 0.95 mg/l (31; 62.5; 125; 250; 500 ppm)
Control Group: Yes, concurrent no treatment
NOAEL: .06 mg/l
LOAEL: .12 mg/l
Method: Other
Year: **GLP:** No
Test substance: No data
Remark: The study was used as a pretest for the 13-week study. 5 males and 5 females were used per group. After the 3rd day of exposure, the urine of the animals was collected for 16 hours. The following parameters were determined in the urine: volume, pH, glucose, protein and activities of aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (AP). One day after the end of exposure, blood samples were taken and examined. The animals and their organs (liver, thymus, right kidney, right testis, heart and lungs) were examined by gross pathology, and the respiratory organs were also examined histopathologically.
Result: In the highest dose group, three males and one female died on the 10th day of exposure. The body weights at the end of the study were significantly reduced in the males of the two highest dose groups and in the females of the highest dose group. In the two highest dose groups, clinical signs typical of substances which irritate the respiratory tract were observed: nasal discharge, increased preening, hypoactivity and labored breathing. In the highest dose group, corneal opacities were detected in the animals exposed during the study; at necropsy, this effect was however confirmed gross-pathologically and histopathologically in only one male. There were no relevant substance-induced influences on the blood pH, coagulation and serum electrolyte concentrations. At the two highest dose levels, urinalysis showed a reduction in the volume of the 16-hour urine in the animals of both sexes and a simultaneous increase of the specific density due to this. The absolute and relative thymus weights were significantly reduced in animals of both sexes of the highest dose group. The other absolute organ weights did not show any significant changes. The relative kidney weight was significantly increased in animals of both sexes, and the relative heart weight was increased only in the females of the highest dose group.

Histopathologic changes were detected in the upper respiratory tract in animals of both sexes from a test substance concentration of 0.12 mg/l (62.5 ppm) onward in relation to the dose. Up to a concentration of 0.48 mg/l (250 ppm), squamous epithelial metaplasias, inflammations and necroses of the respiratory epithelium as well as necroses of the olfactory epithelium were detected. In the highest concentration, the severest lesions also were squamous epithelial metaplasias and inflammations in the larynx. There were no substance-induced histopathologic changes in the lowest dose.

To sum up, the inhalation of the test substance only led to slight effects of systemic toxicity; the histopathologic changes observed were typical of the inhalation exposure of irritant substances.

Test substance: Formic acid, approx. 95% with approx. 5% water

11-SEP-1995 (80) (81)

Species: Rat **Sex:** No data
Strain: No data
Route of admin.: Oral feed
Exposure period: 5-6 weeks
Frequency of treatment: Continuously with the feed
Post. obs. period: No data
Doses: 0.5 and 1.0% (= 2500 mg/kg/d according to the authors, no information whether 0.5 or 1.0%)
Control Group: Yes, concurrent no treatment
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: Cited according to: Sporn, A. et al.: Igiena (Bucharest) 11, 507-515 (1962)
Result: 8 animals were used per group. Retarded body weight gain, reduction of the organ weights (liver and kidneys in both dose groups, adrenal and spleen in the lowest dose group only), no dose dependence.

The results are only available as a brief keynote summary (secondary citation).

11-SEP-1995 (50)

Species: Rat **Sex:** Male/female
Strain: No data
Route of admin.: Drinking water
Exposure period: Up to 27 weeks
Frequency of treatment: Continuously in the drinking water
Post. obs. period: No data
Doses: 8.2, 10.25, 90, 160, 360 mg/kg/d
Control Group: No data specified
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Result: Group 1: 0.01% in the feed for 11 weeks, 6 animals, 8.2 mg/kg/d.
Group 2: 0.01% in the feed for 14 weeks, 3 animals, 10.25 mg/kg/d.
Group 3: 0.1% in the feed for 15 weeks, 6 animals, 90 mg/kg/d.
Group 4: 0.01% in the feed for 12 weeks and subsequently 0.25% for 15 weeks, 4 animals, 160 mg/kg/d.
Group 5: 0.1% in the feed for 17 weeks and subsequently 0.5% for 9 weeks, 3 animals, 360 mg/kg/d.

Reduction of feed consumption and growth in the highest dose (group 5). Mortality: 1/6 and 2/4 in groups 1 and 4 respectively, otherwise no mortality.
The results are only available as a brief keynote summary or as a table in the original literature (Solmann (1921)). The study does not comply with criteria valid today.
11-SEP-1995 (50) (82)

Species: Rat **Sex:** Male/female
Strain: Wistar
Route of admin.: Drinking water
Exposure period: Lifelong (2-3 years)
Frequency of treatment: Continuously in the drinking water
Post. obs. period: None
Doses: 0.2 and 0.4% (= 150-200 mg/kg/d in the lowest dose according to the authors)
Control Group: Yes, concurrent no treatment
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Remark: The results are only summarized in keynotes or presented briefly in a table in the case of body weight gain.
Result: 6 animals were used per group.
No clinical or pathologic changes (growth or organ functions) were detected in any dose group; in particular, there were no disorders of the ocular fundus. The

study includes several generations (up to 5). At the beginning, 8 males and 24 females were used.
Test substance: Ca formate in the drinking water
06-SEP-1995 (56)

Species: Rat **Sex:** No data
Strain: Wistar
Route of admin.: Drinking water
Exposure period: 1.5 years
Frequency of treatment: Continuously in the drinking water
Post. obs. period: None
Doses: 1% (= 274 mg/animal formate or 185 mg/animal calculated to formic acid according to the authors)
Control Group: No data specified
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Remark: The results are only available as a brief keynote summary.
Result: No toxicity detected
6 animals/group
Test substance: Na formate in the drinking water
06-SEP-1995 (56)

Species: Rat **Sex:** No data
Strain: No data
Route of admin.: Drinking water
Exposure period: 6 weeks
Frequency of treatment: Continuously in the drinking water
Post. obs. period: No data
Doses: 0.5 and 1.0% (approx. 2500 mg/kg/d according to the authors; no information whether 0.5 or 1.0%)
Control Group: Yes, concurrent no treatment
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Remark: Cited according to: Sporn, A. et al.: Igiena (Bucharest) 11, 507-515 (1962)
Result: 8 animals were used per group. Reduced body weight gain, reduction of organ weights (liver, kidney and adrenal in both dose groups and spleen only in the lowest dose group); no dose dependence

The results are only available as a brief keynote summary (secondary citation).
11-SEP-1995 (50)

Species: Mouse **Sex:** No data
Strain: B6C3F1
Route of admin.: Inhalation
Exposure period: 13 weeks
Frequency of treatment: 5 days per week, 6 hours per day
Post. obs. period: None
Doses: 0.015; 0.030; 0.061; 0.122; 0.244 mg/l (8, 16, 32, 64, 128 ppm)
Control Group: Yes, concurrent no treatment
NOAEL: .06 mg/l
LOAEL: .12 mg/l
Method: Other
Year: **GLP:** No data
Test substance: No data
Remark: 10 males and 10 females were used per group. The body weights were determined at the beginning and at the end of the study and at weekly intervals in between. The organ weights (thymus, heart, right kidney, lungs, liver and right testis) were determined. At the end of the study, the animals were examined by gross pathology. Some organs were assessed gross-pathologically and histopathologically.
Result: According to the authors, there were no clinical signs of toxicity throughout the study, nor was there any mortality due to exposure. The table shows, however, that only 9 of 10 males and females in each case survived in the highest dose group; the authors do not give any further details. The body weight gains were significantly reduced in the animals of both sexes in the highest dose group, and in the females they were still significantly reduced even in the 64 ppm group. In the highest dose group, the body weights at the end of the study were significantly reduced in the animals of both sexes; this also led to increased relative organ weights in some cases. However, slight, significant increases of the relative liver or kidney weights were detected in the males or females of the 32 and 64 ppm groups.
No gross-pathologic changes were observed. Minimal histopathologic lesions (degenerations) were only observed at the olfactory nasal epithelium in some animals of the two highest dose groups.

According to the NTP, a NOAEL of 64 ppm (0.122 mg/l) is obtained from the results of the 13-week study; taking into account the 2-week study (q.v.), however, the NTP fixed a NOAEL of 32 ppm (0.06 mg/l).
Test substance: Formic acid, approx. 95% with approx. 5% water
11-SEP-1995 (80) (81)

Species: Mouse **Sex:** Male/female
Strain: B6C3F1
Route of admin.: Inhalation
Exposure period: 12 days
Frequency of treatment: 5 days per week, 6 hours per day
Post. obs. period: 1 day
Doses: 0.06; 0.12; 0.24; 0.48; 0.95 mg/l (31; 62.5; 125; 250; 500 ppm)
Control Group: Yes, concurrent no treatment
NOAEL: .06 mg/l
LOAEL: .12 mg/l
Method: Other
Year: **GLP:** No
Test substance: No data
Remark: The study served as a pretest for the 13-week study. 5 males and 5 females were used per group. The animals and their organs (liver, thymus, right kidney, right testis, heart and lungs) were assessed by gross pathology, and the respiratory organs were also examined histopathologically.
Result: All animals of the highest dose group died during the first week of the study; one female of the 250 ppm group (0.48 mg/l) had to be sacrificed on the 4th day on account of its moribund state. At the end of the study, the body weights of the animals of both sexes were significantly reduced in the 250 ppm group. Clinical signs of toxicity due to exposure were only observed in the two highest dose groups and were typical of the exposure to irritant substances by inhalation as in the case of the study with rats. Corneal opacities were observed in the males and females of the highest dose group.
The deaths that occurred were attributed to swelling of the nasal mucosa up to nasal occlusion and severe impairment of respiration due to this. No gross-pathologic changes were observed in any other animals at necropsy at the end of the study. The relative kidney weights of the males of the 62.5, 125 and 250 ppm groups and of the females of the 250 ppm group were slightly increased. In the 250 ppm group, the absolute and relative thymus weights were reduced in animals of both sexes and the relative lung weights were slightly increased. The histopathologic changes showed no substantial sex-specific differences and, except for the highest dose group, they were detected only in the nasal passages. The severity of the histopathologic changes observed (squamous epithelial metaplasias, inflammation and necroses) was dose-dependent, and larynx, pharynx and trachea were also affected in the highest dose group. The males of the two lowest doses showed no changes due to exposure; two females

of the 62.5 ppm group demonstrated squamous epithelial metaplasias of the respiratory epithelium. No histopathologic changes were observed in the lowest dose.

To sum up, inhalative exposure to the test substance only led to slight systemic toxicity; the histopathologic changes observed were typical of the inhalation of irritant substances. When comparing the species, the mouse proved to be more sensitive than the rat.

Test substance: Formic acid, approx. 95% with approx. 5% water

11-SEP-1995 (80) (81)

Species: Mouse **Sex:** No data
Strain: Swiss
Route of admin.: Dermal
Exposure period: 50 days
Frequency of treatment: Twice per week
Post. obs. period: None
Doses: No data
Control Group: Yes, concurrent no treatment
Method: Other
Year: **GLP:** No
Test substance: No data
Remark: The method is not acceptable and does not comply with current criteria. Moreover, documentation is inadequate. Therefore, the study cannot be assessed.
Result: Painting at the ear with 8% formic acid in mineral oil. As compared with tumor promotors (croton oil, Tween 60), no histopathologic or histomorphometric changes

11-SEP-1995 (83)

Species: Dog **Sex:** No data
Strain: No data
Route of admin.: Oral feed
Exposure period: No data
Frequency of treatment: Daily
Post. obs. period: No data
Doses: 500 mg/animal (?)
Control Group: No data specified
Method: Other: No data
Year: **GLP:** No
Test substance: No data
Result: No toxicity detected; no further data. Only secondary citation

06-SEP-1995 (59)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: No data
Metabolic activation: With and without
Result:
Method: Other
Year: **GLP:** No data
Test substance: No data
Remark: Method: Spot test and plate incorporation assay. Bacteriotoxicity was detected; the authors do not make any statement about mutagenicity.
06-SEP-1995 (84)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: 20, 100, 250, 500, 1000, 2000, 2500, 4000, 8000, 12500 ug/plate
Metabolic activation: With and without
Result: Negative
Method: Other: Ames, B.N. et al.: Mutation Research 31, 347-364
Year: 1975 **GLP:** Yes
Test substance: Other TS
Test substance: Calcium formate
23-OCT-1995 (85)

Type: Ames test
System of testing: Salmonella typhimurium TA97, TA98, TA100, TA1535
Concentration: 10, 33, 100, 333, 1000, 3333 ug/plate
Metabolic activation: With and without
Result: Negative
Method: Other: Haworth, S. et al.: Environ. Mutagen. 5, Suppl. 1, 3-142
Year: 1983 **GLP:** No
Test substance: No data
Test substance: Formic acid, approx. 95% with approx. 5% water
06-SEP-1995 (81) (86)

Type: Ames test
System of testing: TA100
Concentration: No data
Metabolic activation: With and without
Result: Negative
Method: Other: Based on Ames, B.N. et al.: Mutation Research 31, 347-364
Year: 1975 **GLP:** No data
Test substance: No data
06-SEP-1995 (87)

Type: Cytogenetic assay
System of testing: CHO-K1 cells
Concentration: 270, 360, 450, 540, 630 ug/ml (6-14 mM)
Metabolic activation: With and without
Result: Ambiguous
Method: Other
Year: **GLP:** No data
Test substance: No data
Remark: Chromosome aberrations were examined. The unbuffered or unneutralized acid was clastogenic at pH values around 6.0 (10-14 mM) and cytotoxic from pH 5.7 (12-16 mM). Clastogenicity is stopped by neutralization with NaOH or by increasing the buffer concentrations in the incubation medium. The authors conclude from this that it is not the substance as such that induces chromosome damage but that the latter is due to the acid pH of the incubation medium as a nonspecific effect.
06-SEP-1995 (88)

Type: Escherichia coli reverse mutation assay
System of testing: Escherichia coli Sd-4
Concentration: 50, 60, 65, 70, 75 ug/ml
Metabolic activation: Without
Result: Positive
Method: Other
Year: **GLP:** No
Test substance: No data
Remark: Weakly positive result (without S9 mix).
The number of bacteria was varied while the test substance concentration remained at almost the same level. The survival rate was reduced with a decrease in the bacterial count (from 100% at 1.5 x 10E9 bacteria up to 2.8% at 2.6 x 10E7). In parallel, the number of mutations was reduced with an increase in the survival rate.
06-SEP-1995 (89)

Type: Mouse lymphoma assay
System of testing: L5178Y mouse lymphoma cells
Concentration: No data
Metabolic activation: No data
Result:
Method: Other: No data
Year: **GLP:** No data
Test substance: No data
Remark: Within the NTP, a mutagenicity test is to be carried out in L5178Y mouse lymphoma cells. No results have been available so far.
07-DEC-1995 (90)

Type: Sister chromatid exchange assay
System of testing: Chinese hamster V79 cells
Concentration: 18.4, 27.6, 46.0, 92.0 ug/ml (0.4, 0.6, 1.0, 2.0 mM)
Metabolic activation: With and without
Result: Negative
Method: Other
Year: **GLP:** No data
Test substance: No data
Remark: No increased SCE frequency with and without S9 mix
08-SEP-1995 (91)

Type: Sister chromatid exchange assay
System of testing: Human lymphocytes
Concentration: 29 - 460 ug/ml (0.63 - 10 mM)
Metabolic activation: Without
Result: Negative
Method: Other
Year: **GLP:** No data
Test substance: No data
Remark: Statistically significantly increased SCE frequency only in the highest concentration (10 mM), otherwise not; however, the pH that is reduced by almost one unit due to the addition of formic acid must be taken into account here.
Test substance: Formic acid, 98-100%
11-SEP-1995 (92)

Type: Other: SOS chromotest
System of testing: Escherichia coli PQ37
Concentration: Up to the solubility limit, but maximally 100 mM (3-5 concentrations)
Metabolic activation: With and without
Result: Negative
Method: Other: Quillardet, P. and Hofnung, M.: Mutation Research 147, 65-78
Year: 1985 **GLP:** No data
Test substance: No data
Remark: In this test system, the SOS gene expression which is induced by DNA damage is measured.
06-SEP-1995 (93)

5.6 Genetic Toxicity 'in Vivo'

Type: Drosophila SLRL test
Species: Drosophila melanogaster **Sex:** Male/female
Strain: Other: Oregon-K
Route of admin.: Other: inhalation and oral feed
Exposure period: 24 h (inhal.); instar and 24 h after hatching (feed)
Doses: No data
Result:
Method: Other: Demerec, M.: Genetics 33, 337-348
Year: 1948 **GLP:** No
Test substance: No data
Remark: Positive after inhalative exposure and administration via the diet with mutation rates of 1.31 and 1.11% as compared with the control limit of 0.15% in each case. If the pH was buffered to 7.5 in the feeding study, there was no increased mutation rate.
06-SEP-1995 (94) (95)

5.7 Carcinogenicity

Species: Mouse **Sex:** No data
Strain: Swiss
Route of admin.: Dermal
Exposure period: 50 days
Frequency of treatment: Twice per week
Post. obs. period: None
Doses: No data
Result:
Control Group: Yes, concurrent vehicle
Method: Other
Year: **GLP:** No
Test substance: No data
Remark: The method is not acceptable and does not comply with current criteria. Moreover, documentation is inadequate. Therefore, the study cannot be assessed.
Result: Painting at the ear with 8% formic acid in mineral oil. As compared with tumor promotors (croton oil, Tween 60), no histopathologic or histomorphometric changes.
06-SEP-1995 (83)

Species: Rat **Sex:** Male/female
Strain: Wistar
Route of admin.: Drinking water
Exposure period: Lifelong (2-3 years)
Frequency of treatment: Continuously in the drinking water
Post. obs. period: None
Doses: 0.2 and 0.4% (= 150 - 200 mg/kg/d according to the authors)
Result:
Control Group: Yes, concurrent no treatment
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Result: No neoplasias were observed. However, the conduct of the study does not comply with current requirements (6 animals per group). See also chapter: Toxicity after repeated administration
Test substance: Calcium formate
06-SEP-1995 (56)

Species: Rat **Sex:** No data
Strain: Wistar
Route of admin.: Drinking water
Exposure period: 1.5 years
Frequency of treatment: Continuously in the drinking water
Post. obs. period: None
Doses: 1% (= 274 mg/animal formate or 185 mg/animal calculated to formic acid according to the authors)
Result:
Control Group: No data specified
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Result: No neoplasias were observed. However, the conduct of the study does not comply with current requirements (6 animals per group). See also chapter: Toxicity after repeated administration
Test substance: Sodium formate
11-SEP-1995 (56)

5.8 Toxicity to Reproduction

Type: Fertility
Species: Rat **Sex:** Male/female
Strain: Wistar
Route of admin.: Drinking water
Exposure Period: Up to 5th (0.2%) or 2nd (0.4%) generation
Frequency of treatment: Continuously in the drinking water
Premating Exposure Period
male: No data
female: No data
Duration of test: Over several generations
Doses: 0.2 and 0.4% (150-200 mg/kg/d according to the authors)
Control Group: Yes, concurrent no treatment
Method: Other: No data
Year: **GLP:** No
Test substance: Other TS
Remark: The conduct of the study does not comply with current criteria. Moreover, documentation is inadequate. Therefore, the study cannot be assessed.
Result: No influence on fertility or offspring over several generations. No indication of teratogenicity. The fertility of the dams, weight at birth and the weight gain of the offspring were measured.
Test substance: Calcium formate
06-SEP-1995 (56)

Type: Fertility
Species: Rat **Sex:** Male/female
Strain: Fischer 344
Route of admin.: Inhalation
Exposure Period: 13 weeks
Frequency of treatment: 5 days per week, 6 hours per day
Premating Exposure Period
male: No mating
female: No mating
Duration of test: 13 weeks
Doses: 0.015, 0.061, 0.244 mg/l (8, 32, 128 ppm)
Control Group: Yes, concurrent no treatment
Method: Other
Year: **GLP:** Yes
Test substance: No data
Remark: 10 males and 10 females were used per group. The investigation was carried out together with a subchronic study (see chapter 5.4). The weight of the left epididymis, sperm motility and concentration or vaginal cytology and estrous cycles were determined.
Result: Formic acid had no effects on sperm motility, sperm concentration, testicular and epididymal weights or on the duration of the estrous cycles due to exposure.
Test substance: Formic acid, approx. 95% with approx. 5% water
08-SEP-1995 (80) (81)

Type: Fertility
Species: Mouse **Sex:** Male/female
Strain: B6C3F1
Route of admin.: Inhalation
Exposure Period: 13 weeks
Frequency of treatment: 5 days per week, 6 hours per day
Premating Exposure Period
male: No mating
female: No mating
Duration of test: 13 weeks
Doses: 0.015, 0.061, 0.244 mg/l (8, 32, 128 ppm)
Control Group: Yes, concurrent no treatment
Method: Other
Year: **GLP:** Yes
Test substance: No data
Remark: 10 males and 10 females were used per group. The investigation was carried out together with a subchronic study (see chapter 5.4). The weight of the left epididymis, sperm motility and concentration or vaginal cytology and estrous cycles were determined.
Result: Formic acid showed no effects on the testicular and epididymal weights or on the duration of the estrous cycles due to exposure. On account of the high motility value of

the control group, sperm motility was reduced in all exposure groups. No substance-induced influences were detected as compared with the historical control.

Test substance: Formic acid, approx. 95% with approx. 5% water

08-SEP-1995 (80) (81)

5.9 Developmental Toxicity/Teratogenicity

Species: Mouse **Sex:** Female
Strain: CD-1
Route of admin.: Gavage
Exposure period: 8th day of gestation
Frequency of treatment: Single dose
Duration of test: Up to the 10th or 18th day of gestation
Doses: 750 mg/kg/d
Control Group: Yes, concurrent vehicle
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Result: In a pilot study, sodium formate was administered in doses of 25, 250, 500 and 750 mg/kg to CD-1 mice by gavage on the 8th day of gestation. The aim was to determine the formate dose necessary to generate a formate concentration in the blood which is achieved after the inhalation of 10,000 ppm methanol for 6h/d. This blood formate concentration was reached at 750 mg/kg.

In the main study with 750 mg/kg, maximally maternal formate concentrations were obtained in the plasma (1.05 mM) and decidua (2 mmol/kg) which were comparable with those after inhalative methanol exposure (10,000 or 15,000 ppm, 6h/d). No significantly increased incidence of CNS defects (open anterior neural tubes) were observed. The red blood count and the decidua folate concentration were unchanged.

The study was carried out to determine the proximal teratogen after exposure to methanol. According to the authors, the present study showed that methanol itself rather than the metabolite formate induced teratogenicity (exencephaly) in pregnant CD-1 mice which were exposed to high methanol concentrations.

Test substance: Sodium formate

30-OCT-1995 (96)

Species: Rat **Sex:** No data
Strain: Sprague-Dawley
Route of admin.: Other: In vitro incubation in WEC (whole embryo culture)
Exposure period: 48 h incubation
Frequency of treatment: Single dose
Duration of test: 48 h
Doses: 200, 400, 800, 1200, 1600 ug/ml
Control Group: Yes, concurrent no treatment
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Result: The effect of the pH (8.13, 7.75, 7.00, 6.50 and 6.00) on the in vitro teratogenicity of sodium formate (0.2, 0.4, 0.8, 1.2 and 1.6 mg/ml) was investigated in rat embryo cultures (Sprague-Dawley rats, day 9.5 of gestation). Numerous embryonic developmental parameters showed that even the decreasing pH had an influence on embryonic development in this test system. In the highest concentration, the parameters crown-rump length (CRL), head length (HL), somite number (SN), developmental score (DS) and protein concentration were significantly reduced in the incubation medium regardless of the pH. At a test substance concentration of 0.8 and 1.2 mg/ml, these parameters were significantly reduced at a low pH. At a test substance concentration of 0.4 and 0.2 mg/ml, CRL, HL and the protein concentration were still significantly reduced at a pH of 6.5 in the medium. To sum up, a dependence of the embryonic developmental parameters and of embryolethality both on the formate concentration and on the pH in the incubation medium was demonstrated in this test system.
Test substance: Sodium formate
30-OCT-1995 (97)

Species: Rat **Sex:** No data
Strain: Sprague-Dawley
Route of admin.: Other: In vitro incubation in WEC (whole embryo culture)
Exposure period: 24 and 48 h incubation
Frequency of treatment: Single dose
Duration of test: 24 and 48 h
Doses: 200, 400, 800, 1200, 1600, 2000 ug/ml (sodium formate) and 140, 270, 540, 810, 1080 ug/ml (formic acid)
Control Group: Yes, concurrent no treatment
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Result: Rat embryo cultures (9th day of gestation) were treated with the test substances. The pH of the medium was no longer corrected after addition of the test substance. Both after 24- and after 48-h incubation with sodium formate, there was a significant and concentration-dependent reduction of the developmental parameters yolk sac diameter (YSD), crown-rump length (CRL), head length (HL), somite number (SN) and developmental score (DEVSC). Embryolethality was significantly increased only in the highest concentration after 48-h incubation. The number of anomalies (mainly CNS: open anterior and posterior neuropores and erratic neurorrhaphy) was significantly increased at 1.6 and 2.0 mg/ml after 24 h and at 0.8 and 2.0 mg/ml after 48-h incubation. The protein and DNA levels showed a significant and concentration-dependent reduction. Incubations with formic acid also showed a significant and concentration-dependent reduction of YSD, CRL, HL, SN and DEVSC after 24-h incubation and of CRL, HL, SOM and DEVSC after 48 h. Embryolethality was significantly increased in the highest concentration after 24 h and in the two highest concentrations after 48 h. Protein and DNA concentrations showed significant and concentration dependent decreases in both cases. The number of anomalies (open anterior and posterior neuropores, rotatory defects and enlarged maxillary process) showed a significant increase only at 0.81 mg/ml after 48-h incubation.
To sum up, concentration-dependent embryotoxic and dysmorphic changes were detected in the culture both using formate and formic acid in this test system.
Test substance: Formic acid and sodium formate
30-OCT-1995 (98) (99)

Species: Mouse **Sex:** No data
Strain: CD-1
Route of admin.: Other: In vitro incubation in WEC (whole embryo culture)
Exposure period: 5 h incubation
Frequency of treatment: Single dose
Duration of test: 5 h
Doses: 45 ug/ml (1 mM)
Control Group: Yes
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Result: The incubation of CD-1 mouse embryo cells (11th day of gestation) in vitro in serum-free medium with 1mM Na formate only led to a very slight, nonsignificant impairment of 3H-thymidine incorporation. Furthermore, the substantial reduction of thymidine incorporation by the teratogenic substance methoxyacetic acid was considerably weakened after the joint incubation with 1mM Na formate.
Test substance: Sodium formate
23-OCT-1995 (100)

Species: Mouse **Sex:** No data
Strain: CD-1
Route of admin.: Other: In vitro incubation in WEC (whole embryo culture)
Exposure period: 24 h incubation
Frequency of treatment: Single dose
Duration of test: 24 h
Doses: 400, 800, 1600, 2000, 3000 ug/ml (sodium formate) and 270, 540, 810, 1600, 2000 ug/ml (formic acid)
Control Group: Yes, concurrent no treatment
Method: Other
Year: **GLP:** No data
Test substance: Other TS
Result: Mouse embryo cultures (8th day of gestation) were treated with the test substances. The pH of the medium was no longer corrected after the addition of the substances. Both with sodium formate and with formic acid, there was a significant and concentration-dependent reduction of the developmental parameters yolk sac diameter (YSD), crown-rump length (CRL), head length (HL), somite number (SN) and developmental score (DEVSC). Embryolethality was not significantly increased in the case of the incubation with sodium formate; there was a significant incidence of anomalies of the CNS (open anterior and posterior neuropores and erratic neurorrhaphy), enlarged pericardium, enlarged maxillary process and retardation in heart development. In the case of the incubation with formic acid, embryolethality was significantly increased in the three highest concentrations; the number of anomalies was significantly increased from a concentration of >=0.54 mg/ml

and was 100% at 1.6 mg/ml. There was a significant and concentration-dependent reduction of protein and DNA concentrations both with sodium formate and with formic acid. YSD, CRL, HL, SOM and DEVSC showed a significant trend to reduction.
To sum up, concentration-dependent embryotoxic and dysmorphic changes were detected in the culture both using formate and formic acid in this test system. In a species comparison with the rat (see entry before), there were no quantitative or qualitative differences.

Test substance: Formic acid and sodium formate

30-OCT-1995 (98) (99)

Species: Mouse **Sex:** No data
Strain: CD-1
Route of admin.: Other: In vitro incubation in WEC (whole embryo culture)
Exposure period: 12 h incubation
Frequency of treatment: Single dose
Duration of test: 12 h
Doses: 180, 360, 540, 900, 1800 ug formate/ml (4, 8, 12, 20, 40 mM)
Control Group: Yes
Method: Other: Cockroft, D.L., in: Copp, A.J. and Cockroft, D.L. (eds.): Postimplantation Mammalian Embryos - A Practical Approach. IRL Press, Oxford, pp. 15-40
Year: 1990 **GLP:** No data
Test substance: Other TS
Result: Mouse embryo cultures (8th day of gestation) were treated with the test substances. The pH of the medium was no longer corrected after the addition of the substances. There was a significant and concentration-dependent reduction of the developmental parameters yolk sac diameter and crown-rump length. Relative embryonic growth and rotation (75% turning in the embryos treated with the test substance as compared with 90% in the control) were retarded. Moreover, concentration-dependent dysmorphogenic effects, such as dysraphia (incomplete closure of the cranium) with a high and significant incidence only in the highest concentration and a developmental disorder of the neural fold were detected.

Test substance: Sodium formate

30-OCT-1995 (96)

Species: Rat **Sex:** No data
Strain: No data
Route of admin.: Other: In vitro whole embryo culture
Exposure period: 48 h incubation
Frequency of treatment: Single dose
Duration of test: 48 hours
Doses: 0-2 mg/ml
Control Group: Yes
Method: Other: No data
Year: **GLP:** No data
Test substance: Other TS
Remark: Effects of the combination of formic acid and methanol were investigated in the whole embryo culture. Gestational day-9 rat embryos were exposed to various concentrations of methanol and formic acid and the degree of embryotoxicity was compared following 48 h of exposure using the developmental score (DEVSC). Increasing concentrations of either methanol or formate resulted in significant decreases in DEVSC. Exposure to the combination of methanol and formate was less toxic than would have been expected based on the single concentration additivity which suggested an antagonistic activity. This observation was found for embryonic crown length, head length, somite number and DNA concentration.
Test substance: Formic acid, probably neutralized, no further data
29-JUL-1997 (101)

Species: Rat **Sex:** No data
Strain: Sprague-Dawley
Route of admin.: Other: In vitro whole embryo culture
Exposure period: 48 h incubation
Frequency of treatment: Single dose
Duration of test: 48 h
Doses: 0.141-1.055 ul/ml (3.74-27.96 umol/ml)
Control Group: Yes
Method: Other: New, D.A.T., The Mammalian Fetus in Vitro, 15-65, CR Austin (ed), Chapman and Hall, London
Year: 1973 **GLP:** No data
Test substance: Other TS
Remark: In the study, the embryotoxicity of methanol and formic acid was evaluated using rat embryo culture. Rat embryos were explanted on day 10 of gestation and cultured. The results obtained showed that both methanol and formic acid have a concentration-dependent embryotoxic effect on the developing embryo in vitro. The no-effect concentration of formic acid was 7.74 umol/ml while a concentration of 18.66 umol/ml was associated with severe embryotoxicity. When embryos were grown in sera containing 18.66 umol sodium formate/ml or in sera adjusted with hydrochloric acid to pH values similar to those achieved with formic acid, the results indicated that both a low pH and formate contributed to the embryotoxicity of formic acid. The authors concluded that embryotoxicity due

to a low pH or a high formate level would occur only after severe methanol intoxication.
Test substance: Formic acid (89-91%), sodium formate
29-JUL-1997 (102)

Species: Rat **Sex:** Female
Strain: Sprague-Dawley
Route of admin.:
Exposure period: Day 9 of gestation
Frequency of treatment:
Duration of test: 48 hours
Doses: 1.51 mg/ml
Control Group: Yes
Method: Other: In vitro incubation in whole embryo culture (WEC)
Year: 1998 **GLP:** No data
Test substance: Other TS
16-MAY-2000

5.10 Other Relevant Information

Type: Adsorption
Remark: Skin penetration; no data usable directly
06-SEP-1995 (103)

Type: Biochemical or cellular interactions
Remark: Title: An in vitro method for predicting sensitizing properties of inhaled chemicals
06-SEP-1995 (104)

Type: Biochemical or cellular interactions
Remark: The authors investigated the concentrations of 10-formyltetrahydrofolate dehydrogenase (FTHFDH) in tissue preparations of the retina, optical nerve and brain of the rat. Here, the authors observed FTHFDH concentrations that suggest high metabolic capacity of the target organs for formic acid. According to the authors, this might be an explanation for the absence of an ocular effect of formic acid (formate toxicity) in the rat.
08-SEP-1995 (105)

Type: Biochemical or cellular interactions
Remark: The study compared the effects on retinal function and structure of rapidly increasing formate concentrations typical of acute methanol intoxication with low level plateau formate concentrations more likely to be generated by subacute or chronic methanol exposure. Anesthetized rats received i.p. injections of methanol at doses of 4 g/kg followed by supplemental injections of 2 g/kg and 1 g/kg respectively at 12-hour intervals. These dosage regimens were designed to maintain blood formate

concentrations ranging from 8-15 mM or 4-6 mM for 30-40 h. Rats that accumulated the hight formate concentration of 8-15 mM developed metabolic acidosis, retinal dysfunction (reductions in a and b waves of the ERG), and retinal histopathologic changes (vacuolation in the retinal pigment epithelium and photoreceptor inner segments). Rats exposed to 4-6 mM for 48 h showed evidence of retinal dysfunction in the absence of metabolic acidosis and retinal histopathology.

Test substance: Methanol, HPLC grade

29-JUL-1997 (106)

Type: Cytotoxicity
Remark: Title: An evaluation of the utility of four in vitro short term tests for predicting the cytotoxicity of individual compounds derived from tobacco smoke

06-SEP-1995 (107)

Type: Cytotoxicity
Remark: Title: Cytotoxicity of carbohydrates heavily irradiated in solution

06-SEP-1995 (108)

Type: Cytotoxicity
Remark: Title: Formic Acid poisoning: Case report and in vitro study of the hemolytic activity

06-SEP-1995 (109)

Type: Cytotoxicity
Remark: Title: Cytotoxicity Testing of 114 Compounds by the Determination of the Protein Content in HEP G2 Cell Cultures

06-SEP-1995 (110)

Type: Excretion
Remark: The urine specimens of 12 male farmers who were exposed to formic acid in a concentration of 0.0073+/-0.0022 mg/l were examined. Immediately after exposure, the excretion of formic acid was not increased as compared with the control group. After 15 and 30 hours, however, there were substantial and significantly increased concentrations of formic acid in the urine of the persons exposed (factor 2.1 and 3.3). Excretion showed a linear dependence on the exposure concentration. The pH in the urine was unchanged, but the ammonium and calcium excretion was significantly increased 30 hours after exposure.

Test substance: Formic acid

08-SEP-1995 (111) (112)

Type: Metabolism
Remark: The following text generally describes the metabolism of formic acid. The citations on which it is based are listed separately with the titles of the studies.
Formic acid is absorbed well via all routes of administration. As a metabolite, it is partially metabolized into CO2 and expired and partially excreted unchanged in the urine in concentrations of 11.7-60 mg/l. The biologic half-life is between 15 minutes and 1 hour:

Formic acid is absorbed from the gastrointestinal tract, via the lungs and the intact skin. The absorbed substance is degraded to carbon dioxide (CO2) and water and is partially excreted unchanged in the urine. The major part of the absorbed formic acid is metabolized in the liver, but partially also in the intestinal mucosa, lungs, kidneys and spleen. Formic acid is oxidized in relation to folate and according to a katalase-peroxidative mechanism. The half-lives of sodium formate in the blood are 12-23, 31-51 and 55 minutes in rats, monkeys and in humans. Formic acid is metabolized into CO2 considerably more slowly in primates than in rats. The species sensitivity to methanol intoxication (metabolic acidosis caused by formic acid) is possibly dependent on the tetrahydrofolate concentration.
08-SEP-1995

Type: Metabolism
Remark: Title: Evaluation of the Health Aspects of Formic Acid, Sodium Formate, and Ethyl Formate as Food Ingredients
06-SEP-1995 (50)

Type: Metabolism
Remark: Title: Kinetics and toxic effects of repeated intravenous dosage of formic acid in rabbits
06-SEP-1995 (113)

Type: Metabolism
Remark: Title: Studies on Methanol toxicity and formate metabolism in isolated hepatocytes
06-SEP-1995 (114)

Type: Metabolism
Remark: Title: Urinary Formic Acid as an indicator of occupational exposure to Formic Acid and Methanol
06-SEP-1995 (115)

Type: Metabolism
Remark: Title: Urinary Excretion of Formic Acid in rabbits
06-SEP-1995 (116)

Type: Metabolism
Remark: Title: Accumulation of Formic Acid in rabbits after daily dosages
06-SEP-1995 (117)

Type: Metabolism
Remark: Title: Pharmacokinetic and deuterium isotope effect studies on the metabolism of formaldehyde and formate to carbon dioxide in rats in vivo
06-SEP-1995 (118)

Type: Metabolism
Remark: Title: Formate in urine as a biological indicator of formaldehyde exposure: A review
06-SEP-1995 (119)

Type: Metabolism
Remark: Title: Formic-Acid excretion in urine as a biological monitoring parameter in areas with different air-pollution
06-SEP-1995 (120)

Type: Metabolism
Remark: Title: Die akute und chronische Toxizitaet der Ameisensaeure und ihrer Formiate
06-SEP-1995 (56)

Type: Metabolism
Remark: Title: Effect of Renal Formic Acid Excretion on Urinary Calcium and Ammonia Concentrations
06-SEP-1995 (121)

Type: Neurotoxicity
Remark: The authors investigated morphologic lesions caused by sodium formate in cell cultures (primary cerebrocortical fetal mouse cells). According to the authors, information on neurotoxicity, gliotoxicity and cytotoxicity is to be obtained from the lesions investigated. Thus, sodium formate showed specific neurotoxicity in concentrations up to 60 mM (2,760 ug/ml) with lesions mainly in the larger polygonal neurons. Concentrations higher than 120 mM (5,520 ug/ml) led to nonspecific cytotoxicity. Furthermore, changes of the membrane integrity were examined via the release of lactate dehydrogenase and 14C-adenine nucleotides and the metabolic activity of the mitochondria.
Test substance: Sodium formate
08-SEP-1995 (122) (123)

Type: Neurotoxicity
Remark: Formic acid was indicated as the neurotoxic metabolite of methanol.
28-JUL-1997 (124)

Type: Toxicokinetics
Remark: The dose-dependent elimination of formate was investigated in the rat using both in vitro and in vivo systems. The in situ perfused liver was used to define the kinetics of hepatic metabolism and obtain initial in vitro estimates of the hepatic metabolism parameters. Formate was eliminated from the perfused rat liver following the Michaelis-Menten kinetics. Estimates of the Michaelis-Menten parameters obtained from the perfused liver studies were used in a two-compartment pharmacokinetic model of the dose-dependent elimination of formate in vivo. A good fit of the model to the observed in vivo data was obtained. Initial estimates of the Michaelis-Menten parameters, Vmax and Km, obtained from the perfused liver model, were within 40% of the final fitted values of these parameters in the in vivo model.
Test substance: Sodium formate, no further data
29-JUL-1997 (125)

Type: Other
Remark: Title:
"A new in vitro method to determine the corrosivity potential of surfactants and surfactant-based formulations"
Test substance: Formic acid
08-SEP-1995 (126)

Type: Other
Remark: Title:
"Penetration of Industrial Chemicals Across the Skin: A Predictive Model"

On the basis of a model system, the test substance was classified as having a toxicologic potential after dermal application.
Test substance: Formic acid
08-SEP-1995 (127)

Type: Other
Remark: For the validation of a new screening test for skin and eye irritation, conventional pretests were carried out with formic acid, among others. In an open patch test in rats and mice, the test substance showed moderate to severe skin irritation in a 10-12% dilution after a dose applied of 100-120 mg/kg. In an intradermal skin irritation test in rats and mice with 2-3% formic acid, similar effects were obtained with doses of 1-1.5 and 10-15 mg/kg. In an eye irritation test in rats and mice with 5-6% formic acid, moderate to severe effects were observed in doses of 2.5-3 and 25-30 mg/kg.

Test substance: Formic acid
08-SEP-1995 (128)

Type: Other
Remark: Title: the role of formate in methanol-induced exencephaly in CD-1 mice
15-MAY-2000 (129)

Type: Other: Carcinogenicity in vitro
Remark: Formic acid did not show any effect on the metabolic cooperation in Chinese hamster V79 lung fibroblasts.
06-SEP-1995 (130)

Type: Other: Chicken egg test
Remark: The method is not acceptable. Moreover, documentation is inadequate. Therefore, the study cannot be assessed.
Result: Sodium formate was injected into the air space of incubated chicken eggs (5, 10 or 20 mg/egg) and these eggs were incubated further up to the 16th day. There was no increased mortality of the embryos. The survival rate was at the same level as that of the controls. The final weights of the embryos of the eggs treated with sodium formate do not reveal any deviations. Sodium formate that was completely eliminated after 10-12 days of incubation, preferably by oxidation, showed no abnormalities with regard to teratogenicity in the incubated chicken egg. As compared with the untreated controls (n=1051), there was no change in the incidence of malformations either quantitatively or qualitatively.
Test substance: Sodium formate
11-SEP-1995 (56)

Type: Other: Human data
Remark: Occupational health study
10 employees in the formic acid filling plant and in the production of urea formaldehyde resin. Inhalation of methanol (40-160 ppm) and formic acid (2-5.5 ppm) at the workplace. Urine concentration of formic acid 16 h after exposure: 21.2-118 mg/g creatinine
07-DEC-1995 (115)

Type: Other: Human data
Remark: Occupational health study
13 farmers when handling silage solution (approx. 80% formic acid)
Increased urine concentration of formic acid 15 h after exposure
(131)

Type: Other: Human data
Remark: Occupational health study
Employees in a textile factory
Formic acid concentration in the air approx. 15 ppm
Subjective complaints about nausea
06-SEP-1995 (132)

Type: Other: Human data
Remark: Case report
45 cases of ingestion of formic acid. Abdominal pain, vomiting, hematemesis, dysphagia, dyspnea, burns in the gastrointestinal tract with subsequent strictures, coagulation disorders, pneumonia, acute kidney failure and hepatic dysfunction. After ingestion of 45-200 g formic acid, 9 of 16 patients died after perforations in the gastrointestinal tract and 5 died of acute kidney failure.
06-SEP-1995 (133)

Type: Other: Human data
Remark: Case report
53 cases of ingestion of formic acid. Burns of the gastrointestinal tract with esophagus strictures, pneumonia, kidney failure, hypotension and unconsciousness
06-SEP-1995 (134)

Type: Other: Human data
Remark: Case report
3 deaths after ingestion of formic acid. Burns in the gastrointestinal tract, metabolic acidosis, coagulation disorders, hemorrhage, shock, hemolysis, respiratory insufficiency and kidney failure. Methemalbumin level 143 mg% (normally 6 mg%) in the blood
06-SEP-1995 (135)

Type: Other: Human data
Remark: Case report
2 cases of ingestion of formic acid. Irritation, edema, blistering and necrosis of the oropharyngeal mucosa.
It was not possible to detect formic acid in the blood or Urine; no methemoglobinemia
06-SEP-1995 (136)

Type: Other: Human data
Remark: Case report
1 death after ingestion of formic acid (approx. 200 ml of an approx. 50% solution). Blood levels of 348 ug/ml of formic acid approx. 2 h after ingestion. Hematemesis, cyanosis, burns in the gastrointestinal tract, shock, metabolic acidosis and hemolysis. In vitro investigation: Hemolysis by acidity
06-SEP-1995 (109)

Type: Other: Human data
Remark: Case report
1 death after the ingestion of formic acid. Hypotension, respiratory insufficiency, coagulation disorders and kidney failure.
06-SEP-1995 (137)

Type: Other: Human data
Remark: Case report
1 case of a local effect of conc. formic acid on the skin. Burns of the legs with subsequent cicatricial changes. Systemic effects: Nausea, vomiting, metabolic acidosis, hemolysis and hemoglobinuria.
06-SEP-1995 (138)

Type: Other: Human data
Remark: Case report
1 case of a local effect of formic acid on the eye. Swelling and opacity of the cornea, pain, lacrimation and contraction of the pupils.
06-SEP-1995 (139)

Type: Other: Mitoses
Remark: Formamide acid 0.1M, 21 hours produce in Pleurodele eggs a dissociation of spindle fibers appears around agglutinated chromosomes.
16-MAY-2000 (140)

Type: Other: Occupational Regulation
Remark: Title: 'Brief introduction to occupational exposure limits in Japan.' In the article, an occupational exposure limit of 5 ppm (9.4 mg/m3) was recommended for formic acid.
Test substance: Formic acid
29-JUL-1997 (141)

Type: Other: QSAR
Remark: Title:
"Quantitative structure activity relationships for skin corrosivity of organic acids, bases and phenols"
Test substance: Formic acid
08-SEP-1995 (142)

Type: Other: Review
Remark: Summary presentations
07-DEC-1995 (70) (50) (143) (144) (51) (71) (72) (52) (73) (59) (145)

Type: Other: Review
Remark: Formic acid irritates the eyes and nasal and pharyngeal mucosas. Direct contact may lead to severe burns to the skin and eyes and in the mouth and pharynx after oral intake. Nausea, vomiting, hemorrhage, acidosis, hemolysis and damage to the heart and central nervous system may occur.
06-SEP-1995 (146)

Type: Other: Review
Remark: One case of an esophagus burn in a child, among others
06-SEP-1995 (147)

Type: Other: Mode of action
Remark: The administration of formic acid in a nonspecified dose to rabbits, dogs and monkeys (presumably via the feed) led to the same histopathologic changes of the retina and the optic nerve as methanol. Acidosis occurred. The authors speculate that the toxic effects might be due to the metabolism of methanol to formic acid via general acidosis. The study is only available as an abstract and the results cannot be assessed.
06-SEP-1995 (76)

Type: Other: Acute toxicity in vitro
Remark: An in vitro model system with Saccharomyces cerevisiae was tested with a total of 160 substances for its suitability as an in vitro model for the determination of the acute toxicity. According to the authors, the IC50 values determined (50% growth inhibition) correlated well with the LD50 values from the literature.
Test substance: Formic acid
08-SEP-1995 (148) (149)

Type: Other: Blood levels
Remark: The formate concentrations were investigated in the blood of 6 volunteers who were administered 200 mg/kg aspartame orally. At the beginning of the study, the formate concentrations were 1.91 +/- 0.61 mg/100 ml, on an average.
Test substance: Aspartame, formic acid
07-DEC-1995 (150)

Type: Other: Blood levels
Remark: The formate concentrations in the blood and urine were investigated in 20 print workers. The aim was to investigate whether the formate concentrations measured allow conclusions to be drawn about the exposure to methanol in the air; the methanol concentrations measured in the respiratory air were 85, 101 and 134 ppm. The formate concentrations in the blood of the workers increased significantly from 3.2 +/- 2.4 mg/l before the beginning of the shift (in the morning) to 7.9 +/- 3.2 mg/l after the shift (in the evening). The specific formate concentrations in the urine increased from 13.1 +/- 3.9 mg/l to 20.2 +/- 7 mg/l. Compared with this, the formate concentrations in the blood of the control persons showed a slight decrease from 5.6 +/- 4.5 mg/l in the morning to 4.9 +/- 4.2 mg/l in the evening; the specific formate concentrations in the urine were 11.9 +/- 6.4 mg/l in the morning and 11.7 +/- 5.6 mg/l in the evening. There was a great interindividual variability of the formate concentrations. According to the authors, the measurement

of the formate concentration in the blood and urine is an important parameter for monitoring the exposure of workers to methanol.

Test substance: Methanol, formic acid

07-DEC-1995 (151)

Type: Other: Final report on the safety assessment of formic acid
Test substance: Formic acid

16-MAY-2000 (152)

Type: Other: Review
Remark: Summary literature

08-SEP-1995 (153) (154)

Type: Other: Review
Test substance: Formic acid

28-JUL-1997 (155)

Type: Other: Review
Remark: Formic acid, draft

15-MAY-2000 (156)

Type: Other: Review - safety assessment
Remark: Final report on the safety assessment of formic acid

15-MAY-2000 (157)

Type: Other: Skin irritation test in vitro
Remark: In an in vitro test system (bovine udder) various substances severely irritating to the skin were investigated. After 2 hours, the tissue was examined biochemically (cytotoxicity and eicosanoid concentrations) and histopathologically. The substances examined had distinct effects on the prostaglandin E2 concentration and on histopathology. According to the authors, further investigations must be carried out to clarify whether slightly skin-irritating substances are also identified in this in vitro test system.

Test substance: Formic acid, 25%

08-SEP-1995 (158)

5.11 Experience with Human Exposure

Remark: Overview: One case of an esophagus burn in a child, among others

(159)

Remark: Overview: Formic acid irritates the eyes and nasal and pharyngeal mucosas. Direct contact may lead to severe burns to the skin and eyes and in the mouth and pharynx after oral intake. Nausea, vomiting, hemorrhage, acidosis, hemolysis and damage to the heart and central nervous system may occur.

(160)

Remark: Occupational health study: When handling silage solution (approx. 80% formic acid), 13 farmers showed an increased concentration of formic acid in the urine 15 h after exposure. (161)

Remark: Occupational health study: After the inhalation of methanol (40-160 ppm) and formic acid (2-5.5 ppm), 10 employees in the formic acid filling plant and in the production of urea formaldehyde resin showed formic acid concentrations of 21.2-118 mg/g creatinine in the urine 16 h after exposure. (162)

Remark: Occupational health study: Employees of a textile factory complained about nausea at concentrations of formic acid of approx. 15 ppm in the air. (163)

Remark: Case report: 45 cases of ingestion of formic acid were described. Abdominal pain, vomiting, hematemesis, dysphagia, dyspnea, burns in the gastrointestinal tract with subsequent strictures, coagulation disorders, pneumonia, acute kidney failure and hepatic dysfunction occurred. After ingestion of 45-200 g formic acid, 9 of 16 patients died after perforations in the gastrointestinal tract and 5 died of acute kidney failure. (164)

Remark: Case report: 53 cases of ingestion of formic acid are described. Burns of the gastrointestinal tract with esophagus strictures, pneumonia, kidney failure, hypotension and unconsciousness occurred. (165)

Remark: Case report: 5 deaths after ingestion of formic acid are described. Burns in the gastrointestinal tract, metabolic acidosis, coagulation disorders, hemorrhage, shock, hemolysis, respiratory insufficiency and kidney failure occurred. The methemoglobin level was 143 mg% (normally 6 mg%) in the blood. (166)

Remark: Case report: 2 cases of ingestion of formic acid are reported. Irritation, edema, blistering and necrosis of the oropharyngeal mucosa occurred. It was not possible to detect formic acid in the blood or urine. There was no methemoglobinemia. (167)

Remark: Case report: One death is reported after ingestion of formic acid (approx. 200 ml of an approx. 50% solution). The blood level is 348 ug/ml formic acid approx. 2h after ingestion. Hematemesis, cyanosis, burns in the gastrointestinal tract, shock, metabolic acidosis and hemolysis occurred.

(168)

Remark: Case report: One death is reported after ingestion of formic acid with hypotension, respiratory insufficiency, coagulation disorders and kidney failure.

(169)

Remark: Case report: One case of a local effect of conc. formic acid on the skin with burns of the legs with subsequent cicatricial changes and nausea, vomiting, metabolic acidosis, hemolysis and hemoglobinuria is reported.

(170)

Remark: Case report: One case of a local effect of formic acid on the eye with swelling and opacity of the cornea, pain, lacrimation and contraction of the pupils is reported.

(171)

Remark: 12 farmers were exposed to an average of 7.3 mg/m3/8h formic acid when handling silage. =0 h after exposure, renal ammonia formation and calcium were increased in the urine.

(172)

Remark: The mean concentration of formic acid in the urine is reported to be 21 mg/l for female and male adults between 20 and 80 years.

(173)

Remark: Case report: After splashing of a drop (0.8 ml 90% formic acid and 0.2 ml 30% hydrogen peroxide) into the eye, there was swelling of the conjunctiva and cornea with complete reversibility after 36-60 hours.

(174)

Remark: From 1989-93, a total of 3 cases of skin and/or eye corrosions after accidental local exposure to formic acid were referred to hospital for further treatment.

(175)

Remark: Twelve male farmers were exposed to 7.3 + 2.2 mg formic acid/m3 for 8 h in silage making. Each gave urine samples immediately, 15h and 30h after the end of the exposure. The excretion of formate was linearly related to the exposure 15 and 30h after exposure. Exposure increased renal ammoniagenesis and urinary calcium at 30h post exposure. Both biochemical effects may be explained by the interaction of formic acid with the oxidative metabolism of renal tubular cells, as formic acid is a known inhibitor of cytochrome oxidase.

25-MAR-1997 (176)

Remark: Report on use of urinary formic acid as a biologic exposure index of methanol exposure.

25-MAR-1997 (177)

Remark: Report on absence of formic acid accumulation in urine following five days of methanol exposure.

25-MAR-1997 (178)

Remark: Report on formic acid excretion in the urine of persons environmentally and occupationally exposed to formaldehyde.

25-MAR-1997 (179)

Remark: Ingestion of over 60 g of formic acid by an adult is potentially fatal. A case of a 36-year-old woman with a history of depression who ingested 110 g of formic acid is reported. She survived a complicated intensive care hospitalization following usage of intravenous folinic acid, urinary alkalinization, intravenous furosemide and supportive care. It is suggested to minimize formate toxicity by enhancing hepatic formate degradation via the folinic acid ¤one carbon pool¤ and by enhanced renal elimination of formate.

25-MAR-1997 (180)

Remark: Systemic toxicity developed in a 3-year-old girl burned by formic acid over 35% of her total body surface area. The patient presented with profound metabolic acidosis and a serum formate level of 400 óg/ml, the highest reported in the literature for poisoning by any route. The patient was successfully treated with hemodialysis, IV bicarbonate, and supportive measures.

25-MAR-1997 (181)

Remark: After inhalation of 200 ppm methanol for 4 h in 22 subjects serum methanol conc. were increased by more than fourfold, as were urinary methanol excretion rates, although formate conc. were not increased over background conc.

25-MAR-1997 (182)

Remark: A case in which a patient sustained an inhalation injury as a result of aerosolized formic acid is reported. The patient sustained a partial thickness burn to the face from a chemical spray; however, as a result of aerosolization, he also inhaled formic acid. This resulted in a reversible pulmonary chemical injury. Inhalation of formic acid results in a reactive airway dysfunction syndrome, a common response to inhalation of an occupational irritant.

25-MAR-1997 (183)

Remark: Compilation of concentrations of drugs affecting digestive system and metabolism. For formic acid the following concentrations in serum/plasma were noted:
Habitual/therapeutic 0-12 µg/ml and toxic 120 µg/ml

Reliability: (4) Not assignable
Only secondary literature

25-NOV-1999 (184)

Remark: Systemic toxicity developed in a 3-year-old girl burned by formic acid over 35% of her total body surface area. The patient presented with profound metabolic acidosis and a serum formate level of 400 µg/ml. The patient was successfully treated with hemodialysis, IV bicarbonate, and supportive measures.

Reliability: (2) Valid with restrictions
Acceptable study, meets basic scientific principles

29-NOV-1999 (185)

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7.1 Risk Assessment

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